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STREPTOCOCCIC AND NONSTREPTOCOCCIC DISEASE OF THE RESPIRATORY TRACT

Epidemiologic Observations

LOWELL A. RANTZ, M.D.
AND
HELEN H. RANTZ
SAN FRANCISCO

PAUL J. BOISVERT, M.D.
NEW HAVEN, CONN.
AND
WESLEY W. SPINK, M.D.
MINNEAPOLIS

DURING the winter of 1943-1944, an extensive study of hemolytic streptococcus sore throat was conducted in a military post. Information in regard to certain aspects of the epidemiology of streptococcic and nonstreptococcic disease of the respiratory tract was obtained and deserves presentation.

The personnel of which the study group was composed changed from time to time, and precise information as to its composition from the standpoint of several of the factors to be considered here was unknown. It was not possible for this reason to determine the true incidence of disease in special groups, but a comparison could always be made between the relative frequency of occurrence of streptococcic and nonstreptococcic infections. It was from this point of view that the following report was prepared.

Study Group.—The study group was the personnel of a military post located in an area in which the incidence of streptococcic disease of the respiratory tract was known to be high. Troop training was of an advanced type, and relatively few of the men had received less than three months of basic training on arrival at the post. Large units, up to and including divisions, were transferred into and out of the post during the study period.

Methods.—All patients with infections of the respiratory tract admitted to the station hospital were studied. Diseased persons were routinely hospitalized if the temperature on examination in the dispensary was greater than 100 F. A history, physical examination and culture materials from the throat were obtained by a

Facilities of the Department of Medicine, Stanford University School of Medicine, were utilized during part of this study.

This investigation was conducted during a field study by the Commission on Hemolytic Streptococcal Infections, Board for the Investigation of Influenza and Other Epidemic Diseases, Preventive Medicine Service, Office of the Surgeon General, United States Army.

member of the commission. Swabs were immediately streaked on horse blood agar plates and incubated for eighteen hours at 37 C. The plates were then examined and the presence or absence of hemolytic streptococci determined. A roughly quantitative estimate of the number of organisms was established. The groups and types of the isolated hemolytic streptococci were determined by the precipitin technic of Lancefield.[1]

Disease.—For the purpose of this study the cases of disease of the respiratory tract were divided into four groups:

1. Hemolytic Streptococcus Sore Throat: Disease of the respiratory tract was assumed to be caused by hemolytic streptococci when the presence of large numbers of these organisms of the Lancefield group A were demonstrated to be present in the nose and/or throat, when the physical examination revealed exudative tonsillitis or great redness and edema of the soft tissues of the throat and especially when definite tender adenitis of the anterior cervical lymph nodes was discovered. In certain cases a scarlatiniform rash was also observed. A significant antistreptolysin and/or antifibrinolysin response occurred in 87.5 per cent of 342 of these patients for whom suitable serial determinations were made, indicating that the clinical diagnosis was usually correct.

2. Nonstreptococcic Disease: Cases of disease of the respiratory tract were included in the nonstreptococcic group if hemolytic streptococci were not recovered from the nose or throat and if the common communicable diseases appeared to be absent. Many of the patients suffered from infections associated with an influenza-like syndrome. Some had mild to severe atypical pneumonia, and others with this disease were undoubtedly given incorrect diagnoses.

3. Indeterminate Group: Two types of cases were included in this group. To the first type belonged those in which the history and physical examination suggested a virus disease of the respiratory tract but in which group A hemolytic streptococci were recovered from the throats of the patients. The organisms were usually present in small numbers, and these cases are believed to represent other types of disease of the respiratory tract occurring in hemolytic streptococcus carriers.

A small number of persons were observed whose histories and features observed on physical examinations were similar to those obtained and observed in instances of hemolytic streptococcus sore throat, but from whose throats these organisms could not be recovered.

4. Miscellaneous: Cases of the common communicable diseases, such as measles, chickenpox and meningococcic meningitis as well as pneumococcic pneumonia, were included in a separate group.

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1. Lancefield, R. C.: Specific Relationship of Cell Composition to Biological Activity of Hemolytic Streptococci, in Harvey Lectures, Baltimore, Williams & Wilkins Company, 1941, vol. 36, p. 251. Precipitin typing serums were supplied in part through the courtesy of Dr. Rebecca C. Lancefield.

The description to follow of certain aspects of disease of the respiratory tract will be confined to those of groups 1 and 2, both of which are large and represent infections in which streptococci definitely were or were not the etiologic agents.

Epidemic Dynamics.—The epidemic dynamics of acute disease of the respiratory tract within the post selected for study over a period of eighteen weeks are presented in chart 1. The incidence of all disease of the respiratory tract for the Service Command in which the post was located is also included.

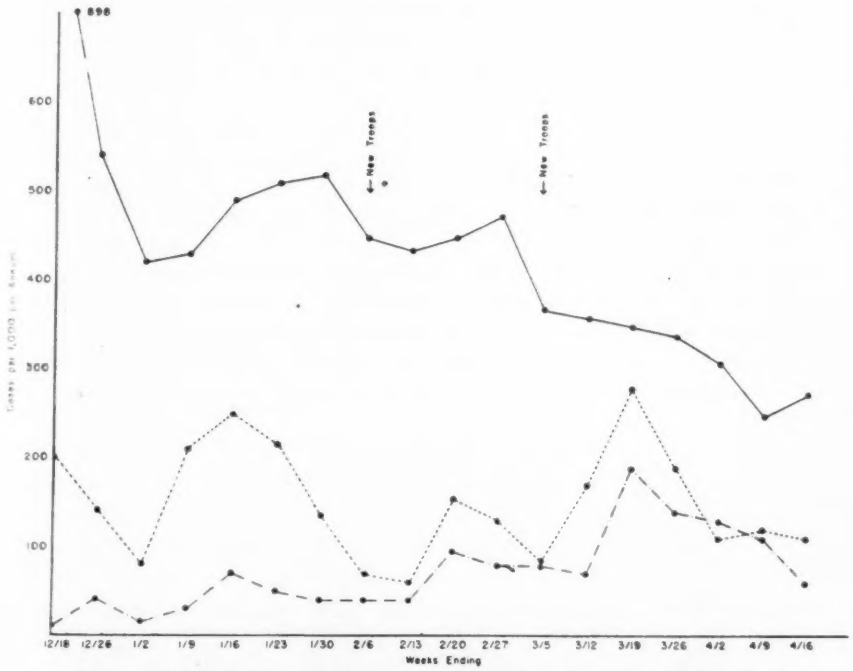

Fig. 1.—Epidemic dynamics of streptococcic and nonstreptococcic disease of the respiratory tract. The solid line indicates the incidence of disease of the respiratory tract in the entire Service Command; the dotted line indicates the incidence of nonstreptococcic disease of the respiratory tract in the post selected for study, and the broken line indicates the incidence of streptococcic disease of the respiratory tract in the post.

A sharp outbreak of influenza A, which was nationwide in its extent, is reflected in the high and rapidly declining rate for disease of the respiratory tract during the last two weeks of December. During January there was an increase in the incidence of disease of the respiratory tract in the Service Command and in the post selected for study. The

characteristic clinical illness during this time was different from that associated with infection by the influenza virus in that it was more protracted and that cough and laryngitis were severe. Neither of these outbreaks was accompanied with or followed over a period of several weeks by an increase in the frequency of occurrence of streptococcic infection. These organisms were responsible for about 25 per cent of all cases during the first six weeks of the study period. At this time nearly all the troops had been stationed in the post for six months or more.

A definite increase in the rates for both streptococcic and nonstreptococcic disease followed the transfer to the camp in the first week of February of a new regiment of seasoned troops from another area. This occurred at a time when the disease rate in the Service Command was approximately stationary and when the outbreak of January had subsided.

In the first week of March a division which had been in training for eight months in an area in which disease of the respiratory tract was rarely observed was transferred to the post. This event was followed immediately by an increase in the frequency of occurrence of nonstreptococcic and, one week later, of streptococcic infection. At the height of the outbreak, which was reached in about two weeks, the infections in 40 to 50 per cent of all cases were caused by streptococci. Four weeks after the influx of new troops the incidence of disease was again low.

Streptococcic Types.—In table 1 the frequency with which each type of streptococcus was involved in the causation of disease is presented.

TABLE 1.—*Distribution of Serologic Types in Cases of Hemolytic Streptococcus Sore Throat*

	Number of Cases		Number of Cases
Not group A	25	Type 18	3
Untypable	59	Type 19	56
Type 1	12	Type 22	1
Type 3	39	Type 24	10
Type 4	1	Type 26	9
Type 5	5	Type 30	24
Type 6	13	Type 32	1
Type 8	2	Type 36	60
Type 9	2	Type 40	1
Type 12	2	Type 41	2
Type 13	1	Type 43	1
Type 14	3	Type 44	9
Type 17	27	Type 46	14

Untypable strains and strains of only thirteen types were responsible for 95 per cent of all streptococcic infections, and the five most common types, 3, 17, 19, 30 and 36, for 57 per cent.

In chart 2 the actual number of infections by any type in 2 or more cases in a week are presented. This chart clearly shows that a true monotype epidemic was never established. During the outbreak in the final month, seven to nine types caused infections in 2 or more cases each

week and from 15 to 25 per cent of the infections were due to the less frequently occurring types.

In January and February, types 3, 17, 19 and 36 were isolated most frequently and types 6 and 44 were not uncommon. Type 30 appeared for the first time in February after a large unit of new troops entered the post. Types 1, 24 and 26 became established with the second influx

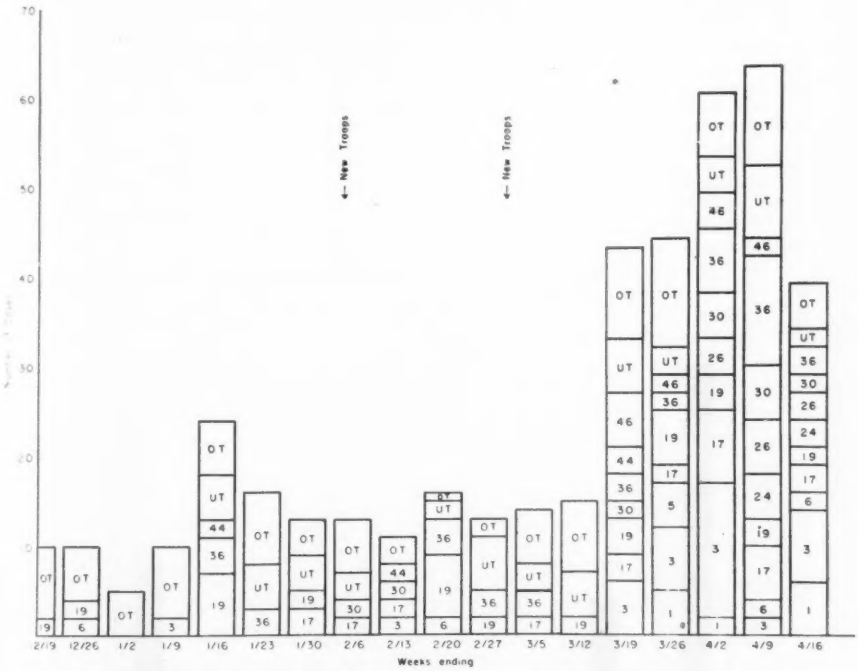

Fig. 2.—Weekly distribution of cases of group A hemolytic streptococcus infection of the respiratory tract by serologic types. *OT* indicates other types; *UT*, untypable.

of troops, in March, but caused relatively little disease. Throughout the study period the strains of the five most common types were the predominating infectious agents.

In one week, 5 cases of infection with type 5 were discovered, and it is of interest to note that the men with these infections had no known contact with one another so far as their military activities were concerned.

Duration of Military Service.—The duration of military service of the members of the total study group was not known, but nearly all the troops had had more than six months of training. This fact is

reflected in the data presented in table 2. Only 10 to 15 per cent of the men suffering from acute illnesses of the respiratory tract had been less than six months in the army, and approximately 50 per cent had been in more than twelve months.

TABLE 2.—*Relation of the Duration of Military Service to the Incidence of Streptococcic and Nonstreptococcic Disease of the Respiratory Tract*

	Nonstreptococcic Disease		Streptococcic Disease	
	Number	Per Cent	Number	Per Cent
0 to 1 month	14	1.7	3	0.7
1 to 3 months	50	5.9	28	6.6
4 to 6 months	56	6.6	11	2.6
7 to 9 months	223	27.4	95	22.5
10 to 12 months	75	8.9	53	12.5
13 to 18 months	174	20.6	122	28.9
19 to 24 months	77	9.1	39	9.2
24 months and up	176	20.8	71	16.8
Total number of cases	845		422	

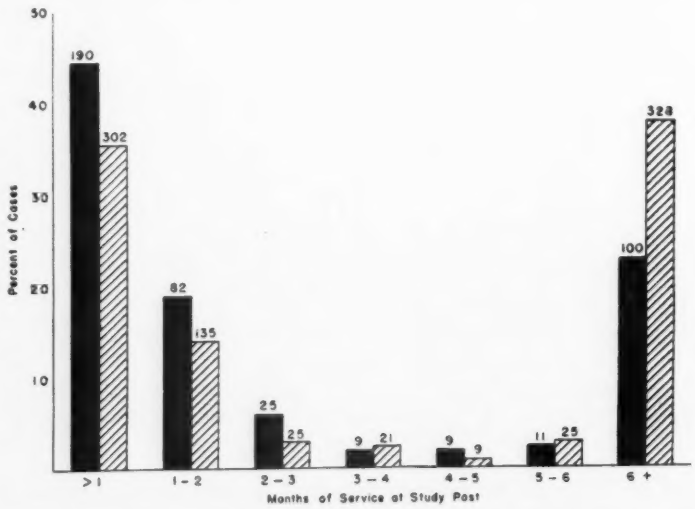

Fig. 3.—Relation between the duration of service in the post selected for study and the incidence of streptococcic and nonstreptococcic disease of the respiratory tract. The solid columns indicate streptococcic disease; the shaded columns, nonstreptococcic disease.

It is also clear that a striking parallelism existed between streptococcic and nonstreptococcic disease in that neither was more likely to occur in men of short military service and that both appeared with about equal frequency in groups with various durations of service.

Duration of Service in Post Selected for Study.—A definite correlation was established between the incidence of disease of the respiratory tract and the length of service at the post selected for study, in contrast to the failure to demonstrate such a relation for the total duration of military service. Chart 3 illustrates this fact. Forty-four and six-tenths per cent of streptococcic infections and 35.8 per cent of nonstreptococcic infections occurred among men who had been in residence in the post for less than one month, and 63.8 per cent and 51.8 per cent, respectively, among those in residence for less than two months.

In this regard it should be borne in mind that approximately 25 per cent of the total cases of streptococcic disease, but 50 per cent of the cases of nonstreptococcic disease, occurred during the first nine weeks of the study, during which time the largest part of the personnel of the post was composed of men who had been stationed there for more than six months.

TABLE 3.—*Relation of Age to the Incidence of Streptococcic and Nonstreptococcic Disease of the Respiratory Tract*

	Streptococcic Disease		Nonstreptococcic Disease	
Age	Number	Per Cent	Number	Per Cent
17 to 20	143	35.0	259	30.7
21 to 24	147	36.0	247	29.6
25 to 30	72	17.6	199	23.6
31 to 35	35	8.6	102	12.1
36 to 40	11	2.7	34	4.0
Over 40	1	0.2	4	0.5

Age.—Inadequate data were available which could be used for the purpose of comparing the actual attack rate in relation to age, since the composition of the study group in this respect was unknown. In table 3 the incidence of streptococcic and nonstreptococcic disease according to age of the affected persons is presented. Most of the infections in both groups were in men less than 30 years old, an incidence which was to have been expected since nearly all enlisted military personnel are in this age group.

Seventy-one per cent of the patients with hemolytic streptococcus infection, but only 60.3 per cent of those with infections not caused by this organism, were less than 24 years of age. Because the number of persons in the study is large, this small difference may be statistically significant.

Premilitary Residence.—The relative frequency of occurrence of streptococcic and nonstreptococcic disease has been compared with the premilitary residence of the infected persons, and no difference in suscep-

tibility to these infections was discovered. The data are presented in table 4.

Rheumatic Fever.—Many cases of rheumatic fever occurred among the personnel of the study post but were insufficient for epidemiologic consideration. Observations reported elsewhere [2] demonstrated that this disorder was invariably a sequel to infection by group A hemolytic streptococci.

TABLE 4.—*Relation of the Premilitary Residence to the Incidence of Streptococcic and Nonstreptococcic Disease of the Respiratory Tract*

Service Command	Approximate Area	Streptococcic Disease		Nonstreptococcic Disease	
		Number	Per Cent	Number	Per Cent
1	New England	42	10.0	75	8.9
2	New York, New Jersey	63	15.2	124	14.6
3	Pennsylvania, Maryland, Virginia	39	9.4	65	7.7
4	South Eastern	49	11.8	114	13.3
5	Southern Great Lakes	45	10.9	135	16.0
6	Western Great Lakes	41	9.9	72	8.5
7	North Central	49	11.8	98	11.6
8	South Central	48	11.6	91	10.8
9	Western	38	9.2	69	8.2

COMMENT

Before the recent war, relatively few studies had been made which permitted a comparison of the epidemiology of hemolytic streptococcic and "virus," or undifferentiated, diseases of the respiratory tract in closed groups containing a homogeneous population. Many reports [3] are available describing outbreaks of hemolytic streptococcus infection, particularly in relation to rheumatic fever.

Dudley [4] has outlined certain basic principles involved in the spread of disease of the respiratory tract in closed groups, which have recently been restated by Coburn [5] with special reference to hemolytic streptococcus infection. The factors involved in the development of epidemics of infection by these organisms were: (1) the frequent introduction of highly susceptible persons into a population with a rapid turnover of personnel; (2) overcrowding, particularly in sleeping quarters;

2. Rantz, L. A.; Boisvert, P. J., and Spink, W. W.: Etiology and Pathogenesis of Rheumatic Fever, Arch. Int. Med. **76**:131 (Sept.) 1942.

3. Paul, J. R.: The Epidemiology of Rheumatic Fever and Some of Its Public Health Aspects, Metropolitan Life Insurance Co. for the American Heart Association, New York, 1943.

4. Dudley, S. F.: The Spread of Droplet Infection in Semi-Isolated Communities, Medical Research Council, Special Report Series, no. 3, London, His Majesty's Stationery Office, 1926.

5. Coburn, A. F., in The Prevention of Respiratory Tract Bacterial Infections by Sulfadiazine Prophylaxis in the United States Navy, Washington, D. C., Bureau of Medicine and Surgery, Navy Department, 1944.

(3) the presence among members of the community of pathogens commonly found in the respiratory tract of an extreme degree of communicability, and (4) outbreaks of measles or influenza which predisposed to infection by streptococci.

Wheeler and Jones [6] have failed to demonstrate that influenza was followed by an increase in the frequency of hemolytic streptococcus disease. A longer period of exposure was required to institute an outbreak of streptococcic infection than to institute one of "virus" infection when new recruits were introduced into a military establishment in which both types of disease were occurring frequently. These authors felt that a constant influx of such susceptible persons was most important for the maintenance of the epidemic state.

Other American investigators [7] have noted that the rapid spread of streptococci occurs more readily in the winter than in the fall. Civilian experience is similar in this country.[3]

This summary provides a suitable background for the consideration of the observations described in this report. The military population from which the study group of infected persons was derived was unstable but of a different nature from those described by others, who have usually considered the problems presented by disease of the respiratory tract in induction stations to which large numbers of recruits highly susceptible to infection are admitted for relatively short courses of training. These troops were nearly all well seasoned men who moved in and out of the post in large groups and who remained for long periods.

The epidemic dynamics of disease of the respiratory tract over an eighteen week period have been described. During the first eight weeks an outbreak of influenza A and another of undifferentiated disease of the respiratory tract, probably not this disease, occurred, neither of which was associated with or followed by an increase in the frequency of streptococcic infection.

The presence in the population of a large number of men who had been stationed in the post selected for study for several months was able to prevent the spread of streptococci, even though "virus" infection was prevalent and the season of the year appropriate. Later, the movement into the post of large groups of men of extended military experience was followed, on two occasions, by an increase in the incidence of undifferentiated disease of the respiratory tract and,

6. Wheeler, S. M., and Jones, T. D.: Factors in the Control of the Spread of Acute Respiratory Infections with Reference to Streptococcal Illness and Acute Rheumatic Fever, Am. J. M. Sc. **209**:58 1945.

7. Hodes, H. L.; Schwenkter, F. F.; Chenoweth, B. M., and Peck, J. L.: Scarlet Fever as an Airborne Infection, Am. J. M. Sc. **209**:64, 1945.

somewhat later, of streptococcic disease. More than 60 per cent of these illnesses occurred among men who had been stationed in the post for less than two months.

Outbreaks of virus infection may, therefore, be expected to occur among well seasoned troops, but it is probable that a definite increase in the frequency of streptococcic infection will be most likely to occur when such men are moved from an area in which disease caused by these organisms is uncommon to one in which it is well established.

Throughout the study period a few serologic types of hemolytic streptococci caused most of the infections. Following the introduction of new troops into the post in the eleventh week, there was an increase in the rate of streptococcic disease, and a few types which had not previously been isolated appeared but were not responsible for many cases. Most of the incoming men appeared to have been infected as the result of exposure to organisms present in the environment on their arrival and not of the enhancement of invasiveness by the new conditions of streptococci already present among them. No tendency toward the establishment of a monotype epidemic was demonstrated.

Since hemolytic streptococci and filtrable viruses are different physically and in many other respects, it was thought that a comparison of the incidence of the diseases caused by these organisms might indicate a difference in the type of host most suitable for each. A comparison of the infected persons on the basis of age, duration of service in the army and length of time in the post studied did not reveal convincing differences, except for the fact that men who had been in the camp for a brief period were more likely to be infected by streptococci.

Because streptococcic disease is believed [8] to be infrequent in the southern United States, it was thought that men whose premilitary residence had been in this area might be more susceptible to infection by these organisms, but they were not.

It may be stated in conclusion that men who had been stationed for a considerable period in the post studied were relatively resistant to infection by streptococci and that the spread of these organisms was not enhanced by preceding virus infection. Fresh seasoned troops were highly susceptible to infection by both agents, and there were no convincing differences in the type of men attacked by either, so far as they have been compared in this study.

SUMMARY

1. Certain aspects of the epidemiology of group A hemolytic streptococcus and nonstreptococcus disease have been studied.

8. Van Ravenswaay, A. C.: The Geographic Distribution of Hemolytic Streptococci: Relationship to the Incidence of Rheumatic Fever, J. A. M. A. **126**:486 (Oct. 21) 1944.

2. Prolonged residence in the post selected for study conferred a considerable resistance to streptococcic infection.

3. Infection by undetermined viruses common to the respiratory tract or by influenza A did not enhance the spread of streptococci.

4. The introduction of well seasoned troops from another area was followed by an increase in the incidence of both streptococcic and nonstreptococcic disease of the respiratory tract.

5. Infection by viruses and by streptococci occurred among men who were similar when compared as to age, duration of military service and premilitary residence.

PROGRESSIVE BILATERAL BULLOUS EMPHYSEMA

ALISON HOWE PRICE, M.D.
AND
GEORGE TEPLICK, M.D.
PHILADELPHIA

APART from emphysema of the bullous type, which is not unusual and occurs in all parts of the lung, there appears to be a different, more uncommon form. Its characteristics are striking enough for one to regard it as an entity, for which we propose the name "progressive bilateral bullous emphysema." The disease is usually recognized after the second decade and is apparently limited to men. The process begins in the apexes and gradually increases, until in extreme cases both upper and lower lobes are replaced by large cystlike areas. The usual history is that of cough, slowly increasing dyspnea, recurrent infections of the respiratory tract, asthma-like attacks and cachexia. Death occurs from intercurrent infections or when insufficient pulmonary tissue is left to carry on normal respiratory exchange.

The following 8 cases were observed in the Jefferson Hospital during a period of three years.

CASE 1.—A 48 year old white painter was admitted to the ward on Oct. 12, 1942, with progressive dyspnea, increasing weakness, chronic cough and susceptibility to colds. There was a 14 pound (6.4 Kg.) loss of weight during the year.

The patient was dyspneic, even at rest. The chest was emphysematous and was hyperresonant to percussion, with distant breath sounds over the upper lobes. The hemoglobin level was 98 per cent, and the erythrocyte count was 4,500,000. The vital capacity was 1,700 cc. A roentgenogram of the chest (fig. 1) on Nov. 11, 1942 showed replacement of the upper lobes with numerous bullae, which compressed the lower lobes. Only a small amount of respiratory tissue remained at the bases. The pulmonary conus was more prominent than normal.

After the aspiration of air from the bullous portion of the left lung, the dyspnea was temporarily relieved. The patient was discharged unimproved on Dec. 24, 1942.

CASE 2.—A 51 year old man entered another hospital in June 1940, with the complaint of increasing shortness of breath and moderate cough with some mucopurulent expectoration. He dated the onset of his symptoms to an attack of pleurisy which had occurred two years before. A roentgenogram taken in June 1940 (fig. *2A*) revealed bullous emphysema of the upper half of both pulmonary fields, more pronounced on the right. Interstitial fibrosis was seen in the hili and the lower pulmonary fields. The heart was normal in appearance. During the next four months he lost 25 pounds (11.3 Kg.) and became weaker.

Examination on his admission to the Jefferson Hospital, Oct. 16, 1940, showed emphysema with distant breath sounds over the upper lobes of both lungs. The

From Jefferson Medical College and the Jefferson Medical College Hospital.

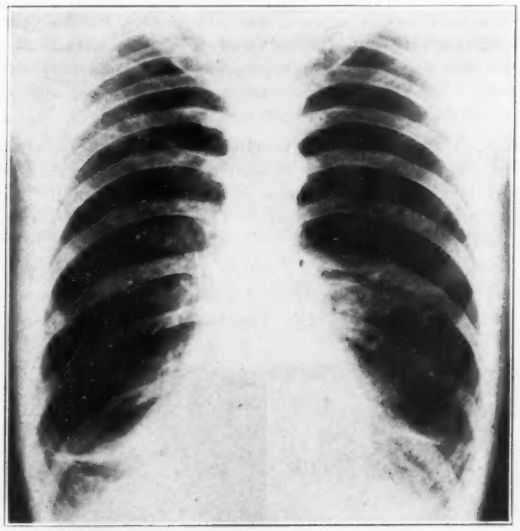

Fig. 1. (case 1).—Prominent pulmonary conus and replacement of upper lobes with numerous bullae, which compress the lower lobes of the lungs.

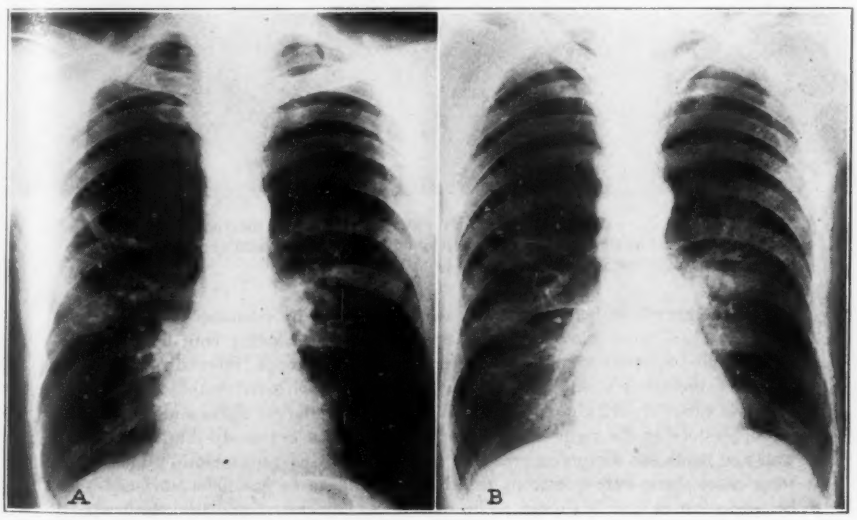

Fig. 2 (case 2).—*A*, roentgenogram taken June 26, 1940. *B*, four months later there are slight increase in the bullous emphysema and development of prominent pulmonary conus.

hemoglobin level was 97 per cent with 4,900,000 erythrocytes. A bronchoscopic examination showed evidence of chronic tracheobronchitis and mucopurulent secretion. A roentgenogram (fig. 2 *B*) showed a slight increase of the bullous emphysema over that shown in the previous film. The pulmonary conus had now become prominent. The patient was symptomatically improved after the bronchoscopic aspiration of 40 cc. of mucopus and was discharged on October 22.

Subsequently all the respiratory symptoms increased in severity, and later roentgenograms (fig. 3) taken at another hospital showed an increase in the bullous emphysema with pneumonitis at the base of the upper lobe of the left lung. The pulmonary conus was even more prominent. The patient died of respiratory failure on March 18, 1942.

Postmortem examination showed a poorly nourished middle-aged white man. The finger nails were curved. The chest was long, and the ribs were curved outward, producing a barrel-shaped chest. The diaphragm was depressed to the level

Fig. 3 (case 2).—*A*, five months after figure 2 *B*, there is increase in emphysema with pneumonitis at the base of the upper lobe of the left lung and greater prominence of the pulmonary conus. *B*, lateral view.

of the seventh rib on both sides. The right pleural cavity contained about 500 cc. of fluid. There were numerous dense fibrous adhesions binding both lungs to the parietal pleura, mediastinum and pericardium. Both lungs, especially the right, contained numerous air-filled emphysematous sacs, which overlay the pericardium. The sacs varied from 2 mm. to 12 cm. in diameter. Two larger bullae almost replaced the upper lobe of the right lung. They consisted of an extremely thin transparent wall and contained air under pressure. The lining tissue was smooth, although in some cases there were numerous thin bands or ridges on the inner surface. The bronchi were uniformly dilated. The mucosa was thickened and dark brown and was covered by a tenacious, thick grayish brown exudate. Careful examination of the bronchi failed to reveal any point of obstruction. The lower lobe of the right lung contained no bullae and was collapsed by the effusion. The pulmonary tissue

elsewhere was soft and grayish pink. The heart weighed 380 Gm. The enlargement was due to hypertrophy and dilatation of the right ventricle and moderate dilatation of the right auricle. The endocardium was smooth. There were a few atheromatous deposits in the substance of the mitral valve. The coronary arteries were patent. There were moderate atherosclerosis of the ascending aorta and a few small plaques on the larger branches of the pulmonary artery. The stomach and remaining portions of the gastrointestinal tract were not unusual. The liver weighed 1,300 Gm. and was not enlarged but had been displaced downward on the right side. A large portion of the capsule on the anterior surface was thickened, smooth and yellowish gray. The cut surface revealed moderate congestion. The gallbladder, bile ducts, pancreas, spleen, adrenal glands, bladder and prostate appeared normal. The kidneys were normal in size, weighing 140 and 150 Gm. On the surface of each kidney were two or three thin-walled cysts 5 to 15 mm. in diameter, filled with clear amber

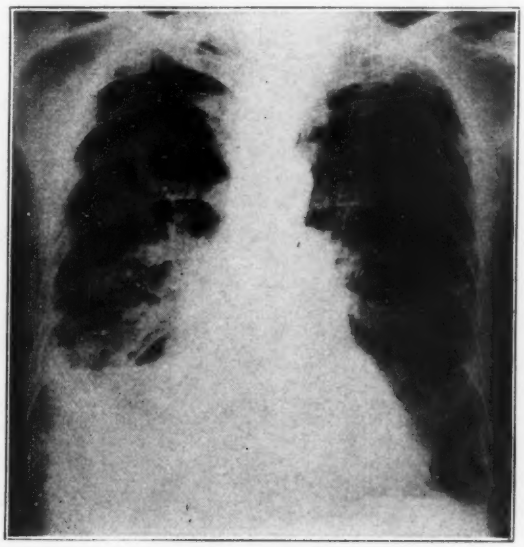

Fig. 4 (case 3).—Extensive bullous emphysema of the upper lobes of both lungs, effusion at the base of the right lung and prominent pulmonary conus.

fluid. The lining was thin and smooth. The cortexes and medullas were otherwise normal.

The anatomic diagnoses were bilateral bullous emphysema of the upper lobes, chronic bilateral fibrous pleuritis, pleural effusion on the right side, hypertrophy and dilatation of the right ventricle, chronic capsulitis of the liver and multiple cortical cysts of the kidneys.

CASE 3.—A 57 year old white merchant was admitted to the hospital on Dec. 26, 1939. He complained of cough and precordial pain of five days' duration and edema of the ankles of two weeks' duration. For two years he had progressive dypsnea and weakness.

Examination showed emphysema of the chest, distant breath sounds over the upper lobes and fine rales at the bases. The heart was enlarged to percussion, and

pretibial edema was present. The blood pressure was 120 systolic and 80 diastolic. Electrocardiographic changes were interpreted as severe myocardial degeneration and right axis deviation. The hemoglobin content was 94 per cent and the erythrocyte count 4,600,000.

A roentgenogram of the chest (fig. 4) showed extensive bullous emphysema of the upper lobes of both lungs. The remaining pulmonary fields were congested, with interstitial fibrosis in the lower lobes. There was an effusion at the base of the right lung. The heart was enlarged, with a prominent pulmonary conus.

Improving with symptomatic treatment, the patient was discharged Jan. 1, 1940.

CASE 4.—A 36 year old white man, a welder, was admitted to the hospital on April 18, 1943. His chief complaint was a chronic cough for fifteen years, asthmatic-like attacks during the past five years and gradually increasing dyspnea. Examination showed an emphysematous chest with occasional rales at the bases. The hemoglobin level was 84 per cent and the erythrocyte count 4,800,000.

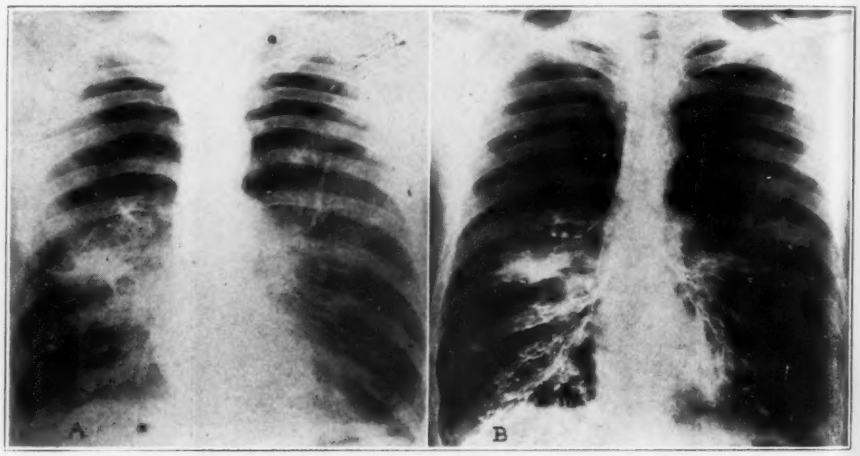

Fig. 5 (case 4).—*A*, emphysema of the upper lobes of both lungs; *B*, a bronchogram demonstrating depression of the bronchial tree and a corrugated appearance of the bronchial tree suggesting early bronchiectasis.

A roentgenogram in 1941 showed advanced bullous emphysema of the upper lobes of both lungs. There was interstitial fibrosis in the lower lobes and hili. The heart had a prominent pulmonary conus but was not enlarged.

The roentgenogram on April 19, 1943 (fig. 5 *A*) showed some increase in the bullous emphysema but no other changes. Bronchoscopic examination revealed chronic inflammatory changes with mucosal thickening in all the main bronchi. A bronchogram (fig. 5 *B*) demonstrated a depression of the bronchial tree by the emphysematous upper lobes. A peculiar corrugated appearance in the entire bronchial tree suggested early bronchiectasis. The patient was discharged May 8, 1943, unimproved.

CASE 5.—A white man aged 49 was admitted to the hospital on Aug. 3, 1943. He complained of cough for twelve weeks with expectoration of mucopurulent

sputum. The cough had become severer. For the past seven years he had had increasing dyspnea, which at the time of his admission occurred with the least exertion. There was vague discomfort in the chest.

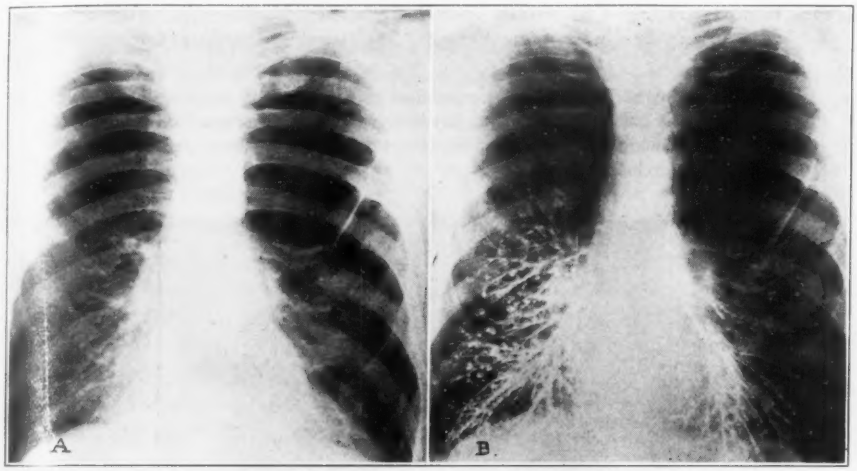

Fig. 6 (case 5).—Extensive bullous emphysema of the upper lobes and bronchogram illustrating depression of the bronchial tree.

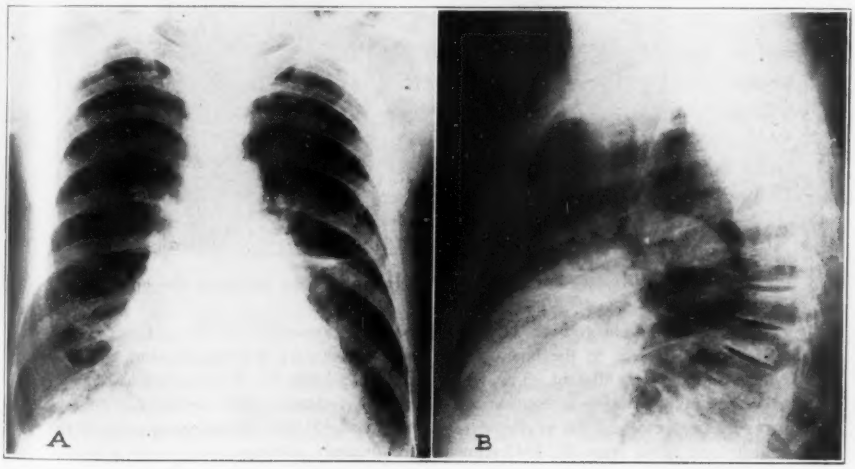

Fig. 7 (case 6).—Moderately enlarged heart with prominent pulmonary conus. *A*, front view and *B*, lateral view.

Examination revealed emphysema with distant breath sounds, especially over the upper lobes. The vital capacity was 2,300 cc. The hemoglobin content was 95 per cent, and the erythrocyte count was 4,800,000. A roentgenogram made two

years before his admission to the hospital showed extensive bullous emphysema of the upper lobes of both lungs with interstitial fibrosis in the lower pulmonary fields. The pulmonary conus was prominent, but the heart was not enlarged. A roentgenogram (fig. 6*A*) on July 7 showed no extension of the bullous involvement. A bronchogram (fig. 6*B*) showed depression of the bronchial tree by bullae of the upper lobes. There was no bronchiectasis. The patient was discharged unimproved on August 31.

CASE 6.—A 62 year old white watchman was admitted to the hospital on Aug. 28, 1943. His chief complaint was gradually increasing dyspnea for thirty years and a mild cough for ten years with expectoration. In the past few weeks mild edema had developed at his ankles.

Fig. 8 (case 8).—Generalized emphysema with giant bullae in the upper lobes.

Examination showed an emphysematous hyperresonant chest, and occasional rales were present in the bases. The heart was enlarged to percussion, and the heart sounds were distant. The vital capacity was 700 cc. The electrocardiogram revealed myocardial degeneration and right axis deviation. The hemoglobin content was 90 per cent and the erythrocyte count was 4,500,000. Roentgenograms of the chest (fig. 7) on Aug. 30, 1943 showed a moderately enlarged heart with a prominent pulmonary conus. Multiple small emphysematous bullae filled the upper pulmonary fields. There was interstitial fibrosis in the lower pulmonary fields. The patient was discharged unimproved.

CASE 7.—A 50 year old white man, a shipper, entered the outpatient department with a complaint of progressive dyspnea for five years. A slight cough had also been present, and he had lost 40 pounds (18.1 Kg.), in the past two years.

Examination revealed slight pulmonary emphysema. The hemoglobin content was 91 per cent. A roentgenogram on Sept. 10, 1943 showed general emphysema with bullous formation in the upper third of the pulmonary fields, more striking on the right. The pulmonary conus was prominent, but the heart was not enlarged. Further studies could not be made.

CASE 8.—A 53 year old white man, a tool grinder, entered the outpatient department, complaining of increasing cough and expectoration for five years. For the past six months he had been getting increasingly dyspneic. He had lost 10 pounds (4.5 Kg.) in the year. Examination showed nothing more than an emphysematous chest. The vital capacity was 2,700 cc. A roentgenogram (fig. 8) showed generalized emphysema with giant bullae in the upper lobes, especially on the left. The heart was not unusual.

COMMENT

The number of features common to these reported cases and to those reported elsewhere favors the view that the disease is an entity. The roentgenographic changes in the lungs are similar in all. In the upper pulmonary fields the walls of the bullae replace the normal markings by a patternless tracery of fine linear shadows. Confluence of some bullae and discreteness of others cause great irregularity of size and shape. In some instances they are high and cystlike, replacing the upper lobe (figs. 1, 2, 5 and 6); in others they are numerous and small (figs. 4 and 7), and in far advanced cases the lower lobes are compressed (fig. 1). The lower pulmonary fields usually show the markings of increased density of interstitial fibrosis. The thorax appears lengthened because of the depressed diaphragm, which draws the mediastinal tissues with it. Bronchography with iodized oil for 2 patients (cases 4 and 5, figs. 5 and 6) showed great depression of the bronchi of the upper lobes by the bullae. The peculiar corrugation of the bronchus in case 4 (fig. 5) suggests the early changes of bronchiectasis. In nearly all cases the pulmonary conus of the heart is enlarged, sometimes with considerable rapidity (case 2, figs. 2 and 3) as a result of an overload on the right side of the heart caused by compression and destruction of much pulmonary tissue.

In the 8 cases of this series and the 13 cases reported elsewhere [1] (table) all the patients were men. The symptoms usually began

1. (*a*) Burke, R. M.: Vanishing Lungs: Case Report of Bullous Emphysema, Radiology **28**:367-371 (March) 1937. (*b*) Jaubert de Beaujeu, A.; Abdallah, T. B., and Picard, P.: Emphysème pulmonaire symétrique à bulles géantes multiples, Presse méd. **48**:283-284 (March 12) 1940. (*c*) Lewis, J.: Chronic Bilateral Spontaneous Pneumothorax, Brit. M. J. **2**:779-780 (Oct. 28) 1933. (*d*) Korol, E., and Ensign, C. F.: Bullous Emphysema? Or Bilateral Pneumothorax? Radiology **23**:223-227 (Aug.) 1934. (*e*) Long, E. R.: Multiple Giant Pneumatoceles of Lung (Giant Bullae of Lung, Bullous Emphysema, Cystic Bronchiolectasis, Polycystic Lung, etc.), Internat. Clin. **3**:1-5 (Sept.) 1940. (*f*) Harris, H. J.: Extensive Destruction of Lungs; Emphysema with Giant Bullae; Autopsy, Radiology **36**:492-

(Footnote continued on next page)

to be obvious in the third and fourth decades; in 1 patient, aged 57, (case 3) symptoms began at 55. In all instances there were cough with some expectoration and increasing dyspnea, and in many, asthma-like attacks, weakness and loss of weight. The prognosis is poor, with slow progression over years and with persistent or recurrent attacks of the symptoms just mentioned. Thus far, the longest periods of observation have been seven years [1g] and eight years.[1f] No case has as yet been reported in which the disease was in the presymptomatic

Summary Data of Cases of Progressive Bilateral Bullous Emphysema

Reported by	Age	Age at Onset	Symptoms			Typical Roentgenologic Findings	Outcome
			Dyspnea	Cough	Asthma		
Lewis [1c] (1933)	49	42	+	..	+	Yes	?
Korol [1d] (1934)	35	25	+	..	..	Yes	?
	37	27	+	+	..	Yes	Slow progression 10 years
Burke [1a] (1937)	28	28	+	+	..	Yes	Progression with death at age 35; autopsy
Kaltreider and Fray [1h] (1939)	35	28	+	+	..	Yes	Died; autopsy revealed anthracosilicosis, fibrosis and bullae
Wiese, Heiken, Charr [1j] (1939)	39	35	+	+	..	Yes	Died; anthracosilicosis, fibrosis and bullae
Beaujeau [1b] (1940)	28	27	+	+	..	Yes	?
Long [1e] (1940)	40	?	..	..	..	None taken	Died; autopsy showed typical bullae
Raman [1g] (1941)	37	36	+	+	..	Yes	?
	40/50	?	+	+	..	Yes	?
	34	27	+	+	..	Yes	Died; no autopsy
Harris [1f] (1941)	41	33	+	+	..	Yes	Died; no autopsy
Allison [1i] (1942)	41	40	+	+	..	Yes	?
Present series:							
Case 1	48	47	+	+	..	Yes	
Case 2	51	49	+	+	..	Yes	
Case 3	57	55	+	..	..	Yes	
Case 4	36	31	+	+	+	Yes	
Case 5	49	37	+	+	..	Yes	Died; autopsy
Case 6	62	32	+	+	..	Yes	
Case 7	50	45	+	+	..	Yes	
Case 8	53	48	+	+	..	Yes	

stage, although one can safely predict that such would be found if mass roentgenography of all patients admitted to hospitals were employed. The progressive nature of this type of emphysema is evident from reported cases, which showed slow progression over a period of

494 (April) 1941. (*g*) Raman, T. K.: Bullous Emphysema of Lung, Indian M. Gaz. **76**:515-516 (Sept.) 1941. (*h*) Kaltreider, N. L., and Fray, W. W.: Pathological Physiology of Pulmonary Cysts and Emphysematous Bullae, Am. J. M. Sc. **197**:62-77 (Jan.) 1939. (*i*) Allison, S. T.: Vanishing Lung: Report of Case of Advanced Bullous Emphysema, Ann. Int. Med. **17**:139-148 (July) 1942. (*j*) Wiese, E. R.; Heiken, C. A., and Charr, R.: Multiple Giant Bullae Associated with Anthracosilicosis, Am. J. Roentgenol. **42**:186-191 (Aug.) 1939.

years.[2] In the case reported by Lewis [1c] there were small translucencies at the apexes with absence of pulmonary markings. This was interpreted as bilateral apical pneumothorax. We have seen 2 similar cases. This may be the earliest manifestation of progressive bullous emphysema. The bullae, apparently, begin in the apexes and gradually extend downward.

Of the 6 fatal cases, reported by others, in all of which the patients were under 42, death apparently resulted from the advancing disease itself. One of our patients died at 51 (table). There was no case studied at necropsy which disclosed a clue to the primary cause of the disease. In 2 cases,[1h] there were anthracosilicosis and perihilar fibrosis. In 1,[1e] simple giant bullae were found and in another [1f] purulent bronchitis and indurated peribronchial tissues, all probably incidental or resultant changes.

The unique appearance of the roentgenogram makes diagnosis relatively simple. The only disease important in differential diagnosis is cystic disease of the lung, in which clearcut rounded cysts are discernible and present anywhere in the lung, not exclusively in the upper lobes.

There is no effective treatment. Prophylactically it would seem desirable to reduce incidental infections of the respiratory tract to a minimum, to prohibit smoking and strenuous labor, to advise living in an equable climate and to observe hygienic measures conducive to good health.

The cause of the condition is unknown. Allison [11] suggested "chronic respiratory strain" resulting from chronic bronchitis and asthma as a factor, but he grouped the disease with ordinary chronic obstructive emphysema. Christi [3] made the following classification of types of emphysema: (1) chronic obstructive or hypertrophic emphysema, in which group Allison [11] has stated that he feels "vanishing lung" belongs; (2) senile or atrophic emphysema; (3) acute vesicular emphysema of the type seen in mountain climbers, which is usually reversible, and (4) localized or compensatory emphysema, most commonly seen in the uninvolved pulmonary fields in patients with pneumonia.

Although long-enduring "respiratory strain" was evident in our patients (cases 4 and 6), it is impossible to tell whether or not the symptoms indicated the cause or were the effect of the form of bullous emphysema present. Furthermore, the existence of either asthma or chronic bronchitis does not explain why men alone were affected or why the disease began bilaterally and in both apexes. The disease may be

2. Raman.[1g] Korol and Ensign.[1d] Wiese, Heiken and Charr.[1j]

3. Christie, R. V.: Emphysema of the Lungs, in Rolleston, H.: British Encyclopedia of Medical Practice, London, Butterworth & Co., Ltd., 1937, vol. 4, pp. 508-519.

a form of chronic obstructive emphysema, but why the bullae should appear where and how they do is a mystery.

The apparent inconsistency that only 13 cases have thus far been reported as such in the literature and 8 cases were observed by us in a short period of three years may be explained partly by the possibility that similar cases may have been reported under a variety of names, such as bullous emphysema, giant bullous emphysema, giant symmetric bullous emphysema, cystic disease of the lungs, multiple cysts of the lung, cystic degeneration of the lungs, vanishing lung and others. The condition is probably far more common than the reported cases indicate, especially in the asymptomatic stage. Personal commentaries from a number of roentgenologists support this view.

SUMMARY

Eight cases of progressive bilateral bullous emphysema are presented, together with a review of 13 cases from the recent literature.

This type of emphysema appears to represent a fairly definite entity, beginning in both apical regions, progressively extending downward and occurring only in males.

Little is known of the cause, pathogenesis or treatment.

It is our opinion that this condition is more prevalent than the literature suggests.

FULMINATING MENINGOCOCCEMIA WITH VASCULAR COLLAPSE (WATERHOUSE-FRIDERICHSEN SYNDROME)

Report on Four Adult Patients Who Recovered

COLONEL D. O. WRIGHT
AND
MAJOR LAURENCE B. REPPERT
MEDICAL CORPS, ARMY OF THE UNITED STATES

NUMEROUS reports during the past two years indicated that the dramatic syndrome of fulminating meningococcic septicemia complicated by severe vascular collapse and widespread purpuric lesions involving the skin and almost any organ, including the adrenal glands, is being more frequently recognized ante mortem. Thomas and Leiphart,[1] in a publication appearing in July 1944, stated: "At the present time almost 150 cases have been reported, the vast majority in infants and young children. A careful search of the literature has revealed only 19 instances in adults." They reported 2 additional fatal cases in which the patients were adults. Prior to the advent of sulfonamide compounds the syndrome was considered universally fatal. In a report appearing in January 1945, Weinberg and McGavack[2] stated that recovery had been reported in only 11 cases of the Waterhouse-Friderichsen syndrome, and they added 1 case in which the patient recovered. A meningococcus was grown on culture of the blood from 6 of the 12 patients, a pneumococcus from 1 and Staphylococcus aureus from 1. For the 4 remaining patients the culture of the blood either showed no growth or was not recorded, but in 2 there were organisms in the spinal fluid.

The purpose of this paper is to report 4 nonfatal cases of fulminating meningococcemia occurring in adults, in which there were organisms grown on culture of the blood and profound vascular collapse—cases clinically indistinguishable from those of the Waterhouse-Friderichsen syndrome. All 4 patients were critically ill, and the prognosis was doubtful for each for a few hours. In addition, we wish to point out: (1) the changing trend of thought concerning pathogenesis, (2) the necessity for early clinical diagnosis and the futility of waiting for

1. Thomas, H. B., and Leiphart, C. D.: Septicemia and Purpura with Adrenal Hemorrhage in the Adult, J. A. M. A. **125**:884 (July 29) 1944.

2. Weinberg, L. D., and McGavack, T. H.: The Waterhouse-Friderichsen Syndrome, New England J. Med. **232**:95 (Jan. 25) 1945.

laboratory aid and (3) the importance of energetic treatment to combat profound shock in this syndrome.

By definition and by popular conception the Waterhouse-Friderichsen syndrome has been considered as a fulminating septicemia which is marked by sudden onset, with hemorrhage in the skin and mucous membranes plus bilateral destruction of the adrenal glands by extensive hemorrhages, resulting in vascular collapse and death. This time-honored conception should be reevaluated, since Williams [3] observed 17 cases of fatal fulminating meningococcic septicemia occurring in children, all with similar clinical observations but in which necropsy revealed bilateral adrenal hemorrhages in only 9. This report forces one to accept one of the following postulates: (1) that the profound vascular collapse or shock is produced by an overwhelming septicemia and that the adrenal hemorrhages are coincidental with hemorrhages elsewhere or (2) that in some cases the vascular collapse is due to the overwhelming septicemia while in others it is due to the combination of septicemia and adrenal hemorrhages. Regardless of which postulate one accepts, septicemia with vascular collapse remains the primary factor, and bilateral adrenal hemorrhage may or may not be added. The former postulate seems more tenable for reasons to be pointed out later, in the comment on pathogenesis.

Based on this reasoning, the attempt to make an early clinical diagnosis without laboratory aid and to start immediate energetic treatment of the profound vascular collapse in conjunction with intravenous administration of sodium sulfadiazine for the septicemia seemed justifiable. Four patients have been seen, who represent 2.6 per cent of all persons with meningococcic infections admitted to this hospital. This figure approximates the 3.3 per cent of 485 cases reported from army camps and cited by Weinberg and McGavack.[2]

PATHOGENESIS

The theory of hemorrhagic destruction of the adrenals, long accepted as the cause of death in this dramatic illness, becomes questionable for several reasons:

1. Thomas and Leiphart [1] pointed out that the explosive development of the Waterhouse-Friderichsen syndrome, which requires but a few hours, is in decided contrast to the slow development of symptoms over a period of a few days in completely adrenalectomized animals. 2. The previously mentioned report of Williams [3] proved that hemorrhagic destruction of the adrenal glands is not the only cause of death, since bilateral adrenal hemorrhage was not revealed at necropsy in

3. Williams, H.: Meningococcal Infections in Infancy and Children, M. J. Australia **2**:557, 1942.

8 of his 17 cases. 3. The therapy with cortical substance in the cases herein reported would not have prevented recurrence of symptoms of adrenal insufficiency if hemorrhagic destruction of the adrenal glands had occurred. 4. If destruction of the adrenal glands had caused the severe vascular collapse in our patients, regeneration could not have been sufficiently rapid to prevent recurrence of symptoms when cortical substance was given for such short periods.

In view of these facts, it is plausible to postulate that the overwhelming septicemia produces severe shock and that if this state remains untreated the shock becomes irreversible, adding to the capillary damage and hemorrhagic manifestations, which coincidentally involve the adrenal glands in some cases.

REPORTS OF CASES

CASE 1.—A white man aged 32 gave a history of becoming acutely ill the night of Jan. 20, 1944, with chilliness, nausea, vomiting, headaches and increasing weakness. He noted a petechial rash the morning of January 21 and was admitted to the hospital at 2:30 p. m.

On admission to the ward he appeared seriously ill. His skin was ashen gray and his lips, fingers and toes cyanotic. His extremities were cold, and he was perspiring profusely. The temperature was 103.6 F.; the systolic blood pressure was 100 mm. of mercury and the diastolic 60. Over the thorax, back and forearms large petechiae were noted. The white blood cells numbered 7,150, with 84 per cent neutrophils. The spinal fluid contained 244 white blood cells, 93 per cent of which were neutrophils. Cultures of the blood and of materials from the throat were made. (It was later reported that they were positive for Neisseria intracellularis, group V.) An infusion of 1,000 cc. of 10 per cent dextrose solution was given. Within an hour after the patient's admission, his pulse had little volume and the systolic blood pressure was 68; the diastolic pressure reading was unobtainable. His neck was not rigid; he was sweating profusely and was restless, sighing and tossing about the bed, and recovery seemed doubtful. Five grams of sodium sulfadiazine, 500 cc. of plasma, 1,000 cc. of 10 per cent dextrose solution and 20,000 units of antimeningococcus serum were given intravenously in rapid succession, and 30 mg. of desoxycorticosterone acetate was given intramuscularly. By 7 p. m. the blood pressure had risen to 100 systolic and 67 diastolic. The pulse volume and the color had improved, but he was still perspiring freely. The purpuric lesions were more extensive, and there was a slight puffiness about the eyelids. He was quiet but apprehensive. An infusion of 1,000 cc. of 10 per cent dextrose solution was given to replace the fluid lost by the profuse perspiration. Between 7 and 11 p. m. there was improvement. The sweating ceased, and his color approached normal. During the night he received 2 Gm. of sodium sulfadiazine intravenously and 15 mg. of desoxycorticosterone acetate intramuscularly and a few hours later 3 Gm. more of sulfadiazine. The systolic pressure varied from 112 to 94. There was a moderate oliguria, with a total fluid intake of 4,180 cc. and an output of only 750 cc.

On January 22 he was much better during the morning; the blood pressure was 94 systolic and 68 diastolic. His color was good; his temperature was 99.2 F. and his pulse 88. Weakness remained, but he was comfortable. Vomiting had ceased, and he was given 1 Gm. of sulfadiazine by mouth every four hours. About

3 p. m. he became apprehensive and restless; the blood pressure dropped to 62 systolic and 40 diastolic. An infusion of 500 cc. of plasma was given. By 8 p. m. he was comfortable again, and the blood pressure was 114 systolic and 68 diastolic. During this twenty-four hour period he received 45 mg. of desoxycorticosterone acetate intramuscularly.

On January 23 he was comfortable and had improved. Systolic pressure varied from 90 to 114 and diastolic from 60 to 64. He received 30 mg. of desoxycorticosterone acetate, which was then discontinued.

On January 24 his condition was excellent; his blood pressure was 110 systolic and 50 diastolic. His later course and recovery were uneventful except for the occurrence of urticaria on January 31, probably due to the antimeningococcus serum.

CASE 2.—A white youth aged 18 gave a history of having experienced headache, fever and a sensation of chilliness for only a few hours before his admission to the hospital at 11 p. m., Jan. 25, 1944. When he arrived in the ward, he did not appear seriously ill. Later in the night he was reexamined; his temperature was 103 F., and a faint petechial rash was noticed. He was again reexamined at 8 a. m. on January 26. He appeared critically ill and drowsy but mentally clear. The petechial rash had increased; the lips, fingers and toes were cyanotic. The extremities were cold, and he was perspiring freely. The blood pressure was 74 systolic and 50 diastolic. The white blood cells numbered 15,210; the spinal fluid was normal. Blood was drawn for culture (later reported as positive for N. intracellularis, group I). Twenty-five milligrams of desoxycorticosterone acetate was given intramuscularly, and 5 Gm. of sulfadiazine was given intravenously, followed by 1,000 cc. of 5 per cent dextrose solution. There was slight objective improvement, and the systolic blood pressure was 82 by 12:45 p. m. Five hundred cubic centimeters of plasma was given intravenously at 1:30 p. m. At 2:45 p. m. the blood pressure was 104 systolic and 63 diastolic. His color had improved, and sweating had ceased. During the night of January 26 the temperature did not exceed 100 F.

By 8 a. m. January 27 he had received a total of 55 mg. of desoxycorticosterone acetate intramuscularly and 10 Gm. of sulfadiazine intravenously. He no longer appeared acutely ill. The temperature was 99 F. and the blood pressure 98 systolic and 50 diastolic. Nausea had ceased, and he was given 1 Gm. of sulfadiazine by mouth every four hours. He received 15 mg. desoxycorticosterone acetate.

On January 28, the temperature was 99 F. and the blood pressure 100 systolic and 50 diastolic. He was given an additional 15 mg. of desoxycorticosterone acetate, which was then discontinued.

The later course was uneventful, and he made a rapid recovery, except that sulfanilamide had to be substituted for sulfadiazine for a thirty-six hour period owing to the appearance of grossly bloody urine.

CASE 3.—A white man aged 28 became suddenly ill with nausea, vomiting, weakness and chilliness about 4:30 p. m. June 1, 1944. He was admitted to the hospital four hours later with a temperature of 103 F. He did not appear seriously ill when examined soon after his admission. The blood pressure was 86 systolic and 52 diastolic and the pulse rate 110. A few scattered petechiae were noted. At 4 a. m. his temperature reached the peak of 107 F. but dropped to 102 F. by 5 a. m.

On June 2 his temperature was 99 F., and the blood pressure was 85 systolic and 50 diastolic at 8 a. m. Petechiae had become more numerous and were present

in the conjunctivas. He was vomiting repeatedly and complained of abdominal pain. With dramatic suddeness, he became apprehensive, restless and progressively weaker. The blood pressure reading was not obtainable at 10.30 a. m. Petechiae were coalescing to form larger purpuric areas. He continued to be restless, perspired profusely and was pale but remained mentally clear. The neck was not rigid. Blood was drawn for culture (later reported positive for N. intracellularis, group II A). Five hundred cubic centimeters of plasma and 5 Gm. of sodium sulfadiazine were given intravenously. Desoxycorticosterone acetate was given hourly, usually in 5 mg. doses. The systolic blood pressure reading was 50 at 1 p. m. and unobtainable at 1:30 p. m. A third infusion of 500 cc. of plasma was given. The systolic blood pressure varied from 0 to 52; the pulse rate was not obtainable at times, and cyanosis was extreme. Twenty milligrams of desoxycorticosterone acetate and a fourth infusion of 500 cc. of plasma were given. At 4 p. m. there was a slight puffiness of the face and eyelids, but there was less cyanosis. The pulse was perceptible, and the blood pressure was 84 systolic and 44 diastolic. Throughout the night periodic vomiting continued, and the systolic pressure varied from 88 to 94. During the twenty-four hour period he received 9 Gm. of sodium sulfadiazine, 8 cc. of an extract of adrenal cortex (Eschatin) and 40 mg. of desoxycorticosterone acetate. The total urinary output was only 780 cc. in spite of an intake of 3,390 cc.

By June 3 he had improved greatly. Nausea had ceased, and he was able to take 1 Gm. of sulfadiazine every four hours by mouth. He complained of pain in the fingers and toes, but swelling and redness were not noticeable. The systolic pressure during the day varied from 90 to 100 and the diastolic from 50 to 70. His temperature did not exceed 100 F., and the pulse rate remained below 100. He received 5 cc. of extract of adrenal cortex and 15 mg. desoxycorticosterone acetate during the twenty-four hour period.

On June 4 he continued to improve subjectively and objectively. No essential change occurred in blood pressure and in temperature. He received 5 mg. of desoxycorticosterone acetate and 4 cc. of extract of adrenal cortex, which was then discontinued. On June 5 improvement was definite. Penicillin therapy was substituted for sulfadiazine owing to a rapidly developing anemia. By June 6 soreness in the fingers and toes had disappeared.

The remaining course was uneventful except for the treatment of the severe anemia and a prolonged convalescence.

CASE 4.—A white youth aged 18 was well on Jan. 20, 1945, but about 1 a. m. on January 21 he was awakened by a sensation of chilliness and nausea. He vomited twice, went back to bed and slept until 6 a. m. During the morning of January 21 he vomited several times; a diarrhea developed, and he felt intensely weak and chilly. He could not clearly recall events that occurred two or three hours prior to his admission to the hospital at 2:30 p. m.

On arriving in the ward he was in a state of shock, was critically ill, restless and apprehensive and was sweating profusely. The blood pressure was 68 systolic and 44 diastolic. The pulse rate was rapid and of poor volume and the temperature 100.8 F. An extensive purpuric rash was noted on the extremities and the trunk. There was no nuchal rigidity, and the lungs were resonant and clear. A clinical diagnosis of fulminating meningococcemia with vascular collapse was made, and treatment was started immediately without waiting for laboratory diagnosis. A continuous infusion of plasma, totaling 1,500 cc., was started. Culture of materials from the pharynx, of venous blood and of materials from petechiae were made (reported positive for N. intracellularis, group II A, at a later date). Five grams of sodium sulfadiazine was given intravenously and

10 mg. of desoxycorticosterone acetate intramuscularly. There was gradual subjective and objective improvement during the following two hours. The blood pressure rose slowly to 99 systolic and 40 diastolic. He became less apprehensive and stated that he felt better. At 6:30 p. m. he was cooperative, quiet, well oriented and less apprehensive. The blood pressure was 92 systolic and 50 diastolic and the temperature 102 F. His face and eyelids appeared slightly puffy. At 10:30 p. m. he complained of feeling weak and continued to vomit periodically. The blood pressure was 88 systolic and 60 diastolic.

On January 22, about 1 a. m., the systolic pressure dropped to 74, and he was more restless and apprehensive. An infusion of 500 cc. of plasma was started, making a total of 2,000 cc. given since admission. He voided a few ounces of dark amber urine, the first since his admission to the hospital. At 6:30 a. m. the blood pressure was 99 systolic and 60 diastolic, but he still complained of being weak. The systolic pressure remained about 90 and the diastolic 60 throughout the day, and there was little change in his condition. Nausea had ceased, and he was given 2 Gm. of sulfadiazine by mouth every four hours.

On January 23 the blood pressure throughout the day varied from 90 systolic and 60 diastolic to 95 systolic and 65 diastolic. The temperature remained approximately 101 F. He complained of pain in the ankles, knees and small joints of the hands and feet, and there was some swelling of the interphalangeal joints. Many of the petechiae had coalesced, forming larger purpuric spots.

On January 24 he was much improved. The dose of sulfadiazine was reduced to 1 Gm. every four hours by mouth. The systolic blood pressure varied from 95 to 100; the temperature was 101 F.

On January 25 the patient looked well. The pains in the joints had improved. The systolic blood pressure remained above 100.

The remaining convalescence was rapid and uneventful.

DIAGNOSIS AND TREATMENT

This syndrome should be included in the differential diagnosis when any patient appears ill to a degree out of proportion to the physical findings, especially if the illness is of less than thirty-six hours' duration. Undue collapse, weakness, restlessness, apprehensiveness, pallor, profuse sweating, vomiting, diarrhea, decreased or decreasing blood pressure and pulse of poor volume may occur in almost any combination and should cause the examiner to institute a diligent search for petechiae, which may be inconspicuous for a few hours. If petechiae are found, a tentative clinical diagnosis of Waterhouse-Friderichsen syndrome should be made and continuous infusion of plasma and adrenal cortex substitution therapy started. Blood should then be obtained for culture and complete blood count. Smears should be made from petechial blood, which may reveal the organism in as high as 83 per cent of cases,[4] and the report of this examination should be available within one to two hours. The severity of the illness, however, dictates that one should give 5 Gm. of sodium sulfadiazine in 1,000 cc. of fluid intravenously

4. McLean, S., and Caffey, J.: Endemic Purpuric Meningococcus Bacteremia In Early Life, Am. J. Dis. Child. **42**:1053 (Nov.) 1931.

without waiting for laboratory aid, because petechial smears will not demonstrate the organisms in approximately one fifth of the cases. The futility of withholding chemotherapy for a report of culture of the blood is ridiculously obvious.

Although one is dealing with a fulminating infection, the absence of fever or the degree of fever at the moment of the examination should not be considered as evidence against meningococcemia. Case 3 emphasizes this point. The patient's recorded temperatures during the first twelve hours of hospitalization were 103, 107, 102 and 99 F.

The amount of sulfadiazine used in treatment of these 4 patients was not excessive. The plan of administration was to give an initial 5 Gm. of sodium sulfadiazine intravenously, followed by 2 or 3 Gm. intravenously every six hours until vomiting ceased and then 1 Gm. of sulfadiazine by mouth every four hours until the temperature had remained normal for three days.

The initial plasma infusion should be continued until there is a definite improvement in the blood pressure. The patient in case 4 received 1,500 cc. initially. In cases 2 and 3 a second drop in blood pressure, which was again controlled by the use of plasma, occurred the day after the patients' admissions. These 2 cases have prompted us to record the blood pressure every thirty to sixty minutes, depending on the severity of the illness at the moment, until the blood pressure has stabilized.

Early diagnosis is imperative if therapy is to be of any value, and in retrospect it appears that a clinical diagnosis could have been made and vascular collapse detected a few hours earlier in 3 of our cases. Therefore, we are routinely recording the blood pressure every thirty to sixty minutes in all proved or suspected cases of meningococcemia in which the patients appear acutely ill, hoping to detect any decided decrease of blood pressure and to institute supportive therapy before the vascular collapse reaches a critical level. Two additional patients have furnished presumptive evidence that this procedure is of value. They appeared seriously ill and had an extensive petechial rash. In both patients the blood pressures fell to 80 systolic and 40 diastolic; their pulse rates were 135 to 140, but their general appearance was not that of shock. An infusion of 500 cc. of plasma promptly restored their blood pressures to normal, and recoveries were uneventful. Adrenal cortex therapy was not employed. We believe these 2 patients might have had severe vascular collapse if plasma had not been given when the systolic blood pressure fell to 80. Fluids by the intravenous route, usually 5 per cent dextrose in an isotonic solution of sodium chloride, were given freely to keep the total intake above 3,500 cc. daily. According to the reports on recovered patients collected and tabulated

by Weinberg and McGavack,[2] the patients received liberal supportive treatment, chiefly in the form of intravenously administered dextrose and sodium hydrochloride solutions. The large fluid intake also helps prevent renal damage from the sodium sulfadiazine given intravenously.

Oxygen therapy is indicated during the first few hours when cyanosis is extreme.

We were not impressed by the beneficial effects, if any, of antimeningococcus serum used in treatment of the patient in case 1 of this report or in the treatment of patients with other types of meningococcic infections.

Substitution therapy with varying amounts of adrenal cortex substance was attempted for a brief period. The patient in case 4 received only one dose of 10 mg. of desoxycorticosterone acetate. Eight of the 10 recovered patients who were reported on by Weinberg and McGavack [2] received adrenal cortex therapy; however, we are not aware of any valid proof of its value or any indication for its use in this syndrome except for the time-honored concept that vascular collapse is due to hemorrhagic destruction of the adrenals. At present, it probably should be used sparingly, and an effort should be made to determine its real value, if any.

SUMMARY

1. Four nonfatal cases of fulminating meningococcemia with severe vascular collapse occurring in adults, clinically indistinguishable from cases of the Waterhouse-Friderichsen syndrome, have been recorded. Treatment consisted of sulfadiazine, large amounts of plasma and fluids intravenously to combat the critical vascular collapse and adrenal cortex substance.

2. Deductive evidence suggests that hemorrhagic destruction of the adrenal glands is not the primary cause of death.

3. Early clinical diagnosis and prompt institution of therapy without waiting for laboratory aid are imperative.

ATYPICAL HEMOLYTIC ANEMIA

Observations with Particular Reference to the Use of Transfusions in the Study of Hemolytic Mechanisms

LIEUTENANT (jg) LAWRENCE E. YOUNG (MC), U.S.N.R.
AND
JOHN S. LAWRENCE, M.D.
ROCHESTER, N. Y.

TWO unusual cases of hemolytic anemia recently studied in the Strong Memorial Hospital presented excellent opportunities for exploring the usefulness of transfusion experiments in the investigation of hemolytic mechanisms.

As a matter of additional interest, the serum of the first patient contained autohemagglutinins active against human cells of all types at body temperature and α_1 agglutinins, active against A_1 cells only. The latter agglutinins have been described in detail in a separate paper [1] devoted to blood subgroups. Some of the features of the second case have also been presented in another publication,[2] which dealt with the in vivo maturation and destruction of the patient's reticulocytes after transfusion to a small child.

It has been amply demonstrated by means of the Ashby technic [3] and its various modifications [4] that transfused normal erythrocytes in the circulation of compatible "normal" recipients disappear in a linear fashion over a period of one hundred to one hundred and forty days.[5]

From the Department of Medicine, University of Rochester School of Medicine and Dentistry, and the Medical Clinic of the Strong Memorial Hospital.

This article has been released for publication by the Division of Publications of the Bureau of Medicine and Surgery of the United States Navy. The opinions and views set forth in this article are those of the writers and are not to be considered as reflecting the policies of the Navy Department.

1. Young, L. E.: Studies of the Subgroups of Blood Groups A and AB: I. Active and Passive Acquisition of Alpha$_1$ Agglutinins as a Result of Transfusion, J. Immunol. **51**:101-110 (Aug.) 1945.

2. Young, L. E., and Lawrence, J. S.: Maturation and Destruction of Transfused Human Reticulocytes, J. Clin. Investigation **24**:554-563 (July) 1945.

3. Ashby, W.: Determination of Length of Life of Transfused Blood Corpuscles in Man, J. Exper. Med. **29**:267-281 (March) 1919.

4. Dacie, J. V., and Mollison, P. L.: Survival of Normal Erythrocytes After Transfusion to Patients with Familial Haemolytic Anaemia, Lancet **1**:550-553 (May 1) 1943.

5. Wearn, J. T.; Warren, S., and Ames, O.: Length of Life of Transfused Erythrocytes, Arch. Int. Med. **29**:527-538 (April) 1922. Wiener, A. S.: Longevity

(Footnote continued on next page)

The cells are destroyed largely in accordance with their age, the oldest cells disappearing first. However, the recent studies of Dacie and Mollison [4] and Brown and associates [6] show that a much more rapid, exponential type of destruction of donated cells occurs following transfusion of normal erythrocytes to patients in whom abnormal hemolytic processes are operating. In these circumstances the cells are destroyed indiscriminately, without respect to their age. These two types of destruction of erythrocytes are illustrated by the hypothetic graph of chart 1.

Brown and associates [6] demonstrated that in simple anemias, such as the so-called idiopathic hypochromic type, nearly all transfused cells were destroyed by a linear process. In acquired hemolytic anemia and after burns, on the other hand, as many as 70 per cent of the cells were destroyed by an exponential mechanism. In other anemias intermediate

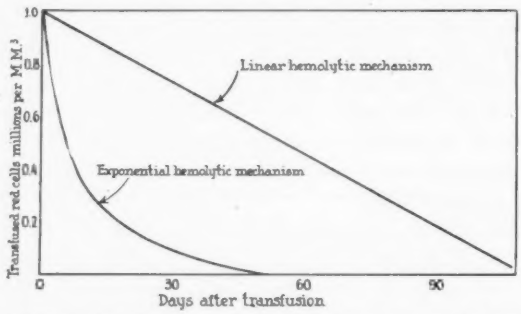

Chart 1.—Hypothetic destruction of transfused erythrocytes by normal (linear) and abnormal (exponential) hemolytic mechanisms (after Brown, Hayward, Powell and Witts [6]).

results were obtained, and in 2 cases a shortened life of the erythrocytes after transfusion was associated with a linear type of decay. It therefore appeared that the manner in which patients disposed of donated cells threw some light on the pathogenesis of their anemia.

Dacie and Mollison [4] found that normal cells had a normal survival time when given to 5 patients with congenital hemolytic jaundice.

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of the Erythrocytes, J. A. M. A. **102**:1779-1780 (May 26) 1934. Wiener, A. S., and Schaefer, G.: Limitations in the Use of Preserved Blood for Transfusion, M. Clin. North America **24**:705-722 (May) 1940. Denstedt, O. F.; Osborne, D. E.; Stansfield, H., and Rochlin, I.: The Survival of Preserved Erythrocytes After Transfusion, Canad. M. A. J. **48**:477-486 (June) 1943. Callender, S. T.; Powell, E. O., and Witts, L. J.: The Life Span of the Red Cell in Man, J. Path. & Bact. **57**:129-139 (Jan.) 1945.

6. Brown, G. M.; Hayward, O. C.; Powell, E. O., and Witts, L. J.: The Destruction of Transfused Erythrocytes in Anemia, J. Path. & Bact. **56**:81-94, 1944.

However, blood taken from 1 of the patients before splenectomy was completely eliminated within fourteen days after transfusion to another person. Normal blood given to the same recipient at the same time survived normally. Erythrocytes taken from the same patient a year after splenectomy likewise disappeared rapidly from the circulation of a normal recipient following transfusion. In the opinion of the authors, these results indicated that the fundamental defect in this disease is the formation of fragile red cells and that this defect persists after splenectomy.

Similar observations were reported by Dacie and Mollison in a case of chronic hemolytic anemia with nocturnal hemoglobinuria. Although an increased rate of destruction of the patient's own cells was evident, transfused normal cells survived normally in the patient's circulation. It was believed that this result supported the view expressed by Ham [7] that the basic abnormality in this disorder is likewise in the erythrocytes, rather than in the serum, spleen or the reticuloendothelial system.

In the first case to be described in this report autologous cells as well as donated normal cells were rapidly destroyed in the patient. This suggested an abnormality of the erythrocyte-destroying mechanism. In the second case transfused normal cells disappeared from the patient's circulation at a normal rate, but the patient's cells were rapidly destroyed after transfusion to a child. Furthermore, the patient's plasma had no hemolytic effect on the cells of a normal recipient. These observations suggested that the abnormality in this case was in the erythron.

The objectives of this report are as follows:

1. To describe in detail the clinical course in 2 unusual cases of hemolytic anemia, both of which might be labeled "acquired" or "atypical" and 1 of which responded to splenectomy.

2. To demonstrate the utility of transfusion experiments in localizing hemolytic abnormalities.

3. To describe the behavior of two irregular agglutinins which may have been responsible for some of the manifestations of the first case.

METHODS

The methods of determining the hematocrit values,[8] the per cent of reticulocytes,[2] acid hemolysis [7] and mechanical fragility [9] of erythrocytes, the serum

7. Ham, T. H.: Studies on Destruction of Red Blood Cells: I. Chronic Hemolytic Anemia with Paroxysmal Nocturnal Hemoglobinuria; an Investigation of the Mechanism of Hemolysis, with Observations on Five Cases, Arch. Int. Med. **64**: 1271-1305 (Dec.) 1939.

8. Wintrobe, M. M.: Macroscopic Examination of the Blood, Am. J. M. Sc. **185**:58-71 (Jan.) 1933.

(Footnotes continued on next page)

bilirubin [10] and fecal urobilinogen concentrations,[11] the Donath-Landsteiner reaction [12] and the presence or absence of autohemolysins and isohemolysins [13] are described elsewhere.

The technics used in tests for osmotic fragility, autoagglutination, isoagglutination and differential agglutination of autologous and of transfused cells will be described subsequently.

REPORT OF CASES

CASE 1.—L. B., a 61 year old white woman, had appeared slightly pale and jaundiced since 1941 but was essentially free of symptoms until late December 1943, when weakness and dizziness were first noted. At that time the patient suddenly became very pale and icteric and was given liver extract and iron, without effect. She was admitted to the Highland Hospital of Rochester, N. Y., on Feb. 25, 1944, at which time the red blood cell count was 1,300,000. The count rose to 3,900,000 after eight transfusions of whole blood, but it soon declined to the original value. The patient was discharged from the Highland Hospital on March 12, 1944. She was readmitted on March 24 for two more transfusions and then was transferred to the Strong Memorial Hospital for further study on March 30.

Family History.—The family history was noncontributory, and detailed examinations of the blood of the patient's two children did not reveal any abnormalities.

Observations on Admission.—The temperature was 102 F., pulse rate 120, respiration rate 30 and blood pressure 118 systolic and 62 diastolic. The patient appeared acutely ill and apprehensive. The skin and mucous membranes were extremely pale, and the skin and scleras were moderately icteric. The heart was slightly enlarged, and there was a systolic, probably hemic, murmur over the entire precordium. The liver and spleen were palpable 4 and 8 cm., respectively, below the costal margin. There was 1 plus pitting edema about the ankles.

Laboratory Observations.—On admission laboratory observations were as follows: red blood cells 1,290,000, hematocrit value 12.3 per cent, hemoglobin value 3.5 Gm. per hundred cubic centimeters; white blood cells 7,450, platelets 132,000 and reticulocytes 33 per cent. The differential count of the leukocytes was normal. There were slight poikilocytosis and moderate anisocytosis of the red cells; the average size of the cells was considerably above normal, and most of the macrocytes were polychromatophilic. Spherocytes and nucleated red cells were not present; search for the former was repeatedly made in wet preparations. Tests for warm and cold hemolysis (Donath-Landsteiner), acid hemolysis (Ham) and sickling yielded negative results. The icterus index was 24, bilirubin (direct test)

9. Shen, S. C.; Castle, W. B., and Fleming, E. M.: Experimental and Clinical Observations on Increased Mechanical Fragility of Erythrocytes, Science **100**:387-389 (Oct. 27) 1944.

10. Malloy, H. T., and Evelyn, K. A.: Oxidation Method for Bilirubin Determinations in Bile and Meconium with the Photoelectric Colorimeter, J. Biol. Chem. **122**:597-603 (Feb.) 1938.

11. Watson, C. J.: Studies of Urobilinogen: I. An Improved Method for the Quantitative Estimation of Urobilinogen in Urine and Feces, Am. J. Clin. Path. **6**:458-475 (Sept.) 1936.

12. MacKenzie, G. M.: Paroxysmal Hemoglobinuria, Medicine **8**:159-191 (May) 1929.

13. Dameshek, W.: The Management of Acute Hemolytic Anemia and the Hemolytic Crisis, Clinics **2**: 118-165, 1943.

1.28 mg., bilirubin (indirect test) 3.64 mg. and nonprotein nitrogen 45 mg. per hundred cubic centimeters, albumin 3.6 Gm., globulin 2.9 Gm. and fibrinogen 0.338 Gm. per hundred cubic centimeters.

Examinations of the urine consistently showed traces of albumin, large amounts of urobilinogen (qualitative tests) and many yellow-brown granular casts. At no time did the patient have hemoglobinemia or hemoglobinuria. Quantitative determinations of fecal and urinary urobilinogen excretion were not obtained. The blood was cultured twice, with negative results. The stool contained no blood, ova or parasites. Wassermann and Kahn reactions were negative.

Course.—The most important events of the patient's stay in the hospital are indicated in chart 2. Febrile reactions had occurred after at least six of the ten transfusions given at the Highland Hospital, and chills and fever followed nearly all twenty transfusions administered at the Strong Memorial Hospital. At no

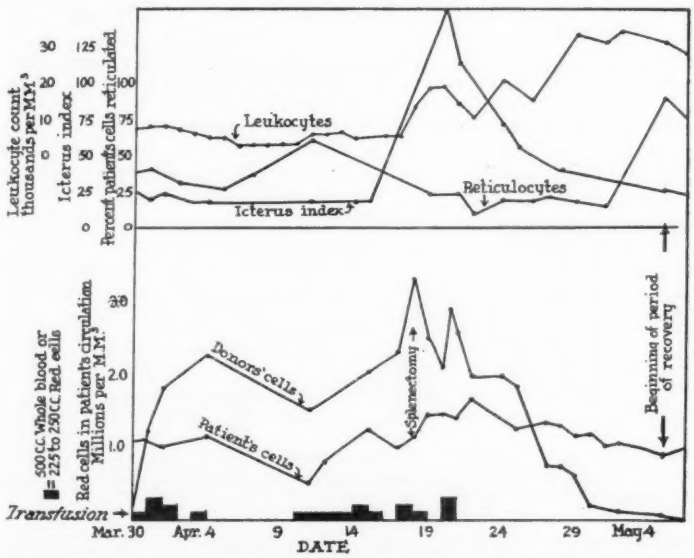

Chart 2 (case 1).—Hematologic changes during patient's hospital stay.

time was the patient completely afebrile, but there was a minimum of fever during the period from April 4 to 9, when no transfusions were given. Rapid destruction of all donated cells as well as of the patient's own red cells was demonstrated by differential agglutination studies, which will be described separately. Because of the rapid elimination of cells, transfusions provided only temporary benefit.

Splenectomy was performed by Dr. J. J. Morton on April 18. The spleen weighed 1,160 Gm.; it was firm and dark red, and six areas of infarction were present. Microscopic examination of the spleen revealed many red cells and collections of dark pigment granules in the venous sinuses. There was hyperplasia in the malpighian bodies, especially in the germinal centers, but no evidence of erythrophagocytosis could be found.

Postoperative Complications.—The early postoperative course was stormy and was marked by rapid destruction of red cells and the development of congestive

heart failure. The icterus index rose to a peak of 150 on April 20, at which time the foam test of the urine elicited a positive reaction for bilirubin, and the serum bilirubin concentration was 9.24 mg. per hundred cubic centimeters direct and 14.7 mg. per hundred cubic centimeters indirect.

The patient was rapidly digitalized on April 20 because of the development of auricular fibrillation and congestive heart failure. A transfusion of 750 cc. of red cells was given slowly on the same day. These measures were followed by temporary improvement, but during the next ten days the course was rapidly downhill and was marked by leukocytosis, hectic fever and phlebothrombosis of several of the superficial veins of the legs. Thrombosis of the splenic vein was also suspected. Additional transfusions were not given because the patient's serum agglutinated cells of all groups at body temperature. At the time of discharge from the hospital on May 2 the prognosis appeared to be grave. On May 5, when a visit was made at the home, the red cell count had fallen to 880,000, and it was demonstrated that nearly 90 per cent of the patient's cells were reticulocytes.

Phase of Recovery.—After May 5 there was steady objective and subjective improvement. The gradual rise of the red cell count and the decrease in mean

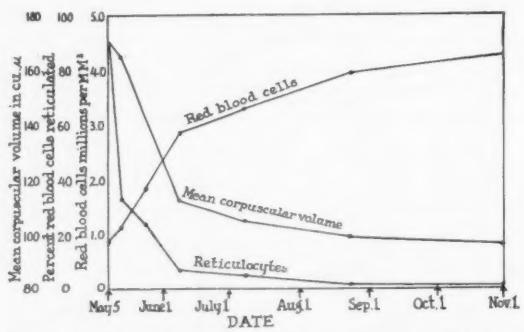

Chart 3 (case 1).—Relation of total erythrocyte count, reticulocyte count and mean corpuscular volume during phase of recovery. Note parallelism between mean corpuscular volume and per cent reticulocytes.

corpuscular volume and in the number of reticulocytes are shown graphically in figure 3. The patient was performing all the usual household duties when last seen, on Oct. 31, 1944. At that time all hematologic values were normal except for the persistence of cold hemagglutinins. Her condition in June 1945 remains good.

Fragility of Erythrocytes.—Fragility of the red cells in hypotonic solutions of sodium chloride was determined on five occasions. Tests were made in two ways. The customary method involved placing 1 drop of oxalated blood [14] into each of a series of tubes containing 1 cc. of saline solution in concentrations ranging from 0.80 per cent to 0.20 per cent. After the contents were mixed, the tubes were placed in the refrigerator overnight and checked grossly for hemolysis the following day. Record was made of the concentration of salt in the first tubes in the series

14. When the plasma was icteric, as in this case, the cells were washed and resuspended with an equal volume of isotonic solution of sodium chloride. The cells of the control blood were treated in the same way.

in which hemolysis was (1) detectable, (2) marked and (3) complete. The readings for normal blood tested in this way were: (1) 0.46 to 0.50 per cent, (2) 0.38 to 0.42 per cent and (3) 0.30 to 0.34 per cent.

On each occasion fragility was also tested by a slight modification of the photoelectric method of Hunter.[15] Ten cubic centimeters of salt solution were placed in each of a series of Evelyn colorimeter tubes, and 0.02 cc. of blood was added to each with a hemoglobinometer pipet. After standing thirty minutes at room temperature the tubes were centrifuged fifteen minutes at 1,500 revolutions per minute. The tubes were then carefully moved to the colorimeter, where the concentration of hemoglobin in the supernatant fluid was determined.

On March 31 and April 3 fragility was somewhat increased. Hemolysis began at 0.69 and 0.56 per cent, respectively, and was marked at 0.48 per cent and complete at 0.32 per cent on both dates. Results with the colorimetric method also indicated that fragility was increased in concentrations of salt between 0.50 and 0.64 per cent. On April 18 and 28 and on May 22 fragility, tested by both methods, was normal.

The mechanical fragility of the cells from this patient was not determined.

Destruction of Transfused Cells.—The fate of erythrocytes donated to this patient was followed closely by means of quantitative differential agglutination tests. The technic employed was that of Ashby[3] as modified by Dacie and Mollison,[4] except that the dilution of the recipient's cells in the initial suspension was 1:101 instead of 1:51. Each mixture of serum and cells was prepared in duplicate, and a separate count of the unagglutinated cells in each tube was made by each of two persons. The count finally recorded was therefore the average of four separate counts of each serum-cell mixture. Total red cell counts were also made in duplicate by two persons and the average of the four counts recorded. Further details of the Ashby technic, as employed in this laboratory, are given elsewhere.[2]

The patient's blood group was A_2MRh+; this was repeatedly confirmed during the convalescent period after all of the donated cells had been eliminated. All but three of the donors were Rh positive.[16] The blood groups of the donors were as follows:

Group	Number of Donors
A_1	21
A_1MN	16
A_1M	4
A_1N	1
A_2	6
A_2MN	4
A_2M	1
A_2N	1
O	3
OMN	1
OM	2
	30

The donations of A_1M and A_2M blood had been given before the patient was transferred to the Strong Memorial Hospital, and these cells had been destroyed by the time the series of differential agglutination tests was begun.[17] Thereafter,

15. Hunter, F. T.: A Photoelectric Method for the Quantitative Determination of Erythrocyte Fragility, J. Clin. Investigation **19**:691-694 (Sept.) 1940.

16. Anti-Rho′ human serum was used for all the Rh tests referred to in his paper. Wiener, A. S.: The Rh Blood Factors, J. A. M. A. **127**: 294 (Feb. 3) 1945.

(Footnotes continued on next page)

group A[17] blood was removed from the bank and given to the patient only if it belonged to type N or MN.

When anti-N serum was added to suspensions of the patient's cells after transfusion of N or MN blood, the donated cells were agglutinated while the patient's cells remained unagglutinated. The latter, free cells, were readily counted after the serum-cell mixture was transferred to a counting chamber. A correction factor of 30,000 cells per cubic millimeter had to be included in the calculations, because this was the average number of cells left unagglutinated after addition of anti-N serum to suspensions of N and MN cells unmixed with M cells. Calculations were carried out according to the following equations:

$$\text{Number of patient's cells} = \text{number cells unagglutinated by anti-N serum} - 30{,}000$$

$$\text{Number donated N or MN cells} = \text{total red cell count} - \text{number of patient's cells.}$$

On April 20, 1944, two days after splenectomy, the patient was given 750 cc. of fresh group O red cells pooled from three donors (OM and OMN). The survival of these cells was studied by the use of B serum, which agglutinated the patient's A_2 cells and the donated A_1 cells (only A_1 cells had been transfused since March 31) and left the O cells unagglutinated. The following calculation was then employed:

$$\text{Number of donated O cells} = \text{number cells unagglutinated by B serum} - 15{,}000.$$

It was necessary to subtract 15,000 cells per cubic millimeter in this equation, because this was the number of cells unagglutinated by B serum before transfusion.

Since absorbed B serum agglutinates A_1 cells but not A_2 cells or O cells, the number of A_2 cells (patient's own cells) present after transfusion of O cells was determined as follows:

$$\text{Number } A_2 \text{ (autologous) cells} = \text{number cells unagglutinated by absorbed B serum} - 35{,}000 - \text{number donated O cells.}$$

A correction of 35,000 cells was made because this was the average number of cells left unagglutinated after absorbed B serum was added to A_1 cells (pooled from the last three A_1 donors used) unmixed with A_2 or O cells. The absorbed B serum had been prepared by absorbing with A_2 cells a very potent B serum from a donor who had been immunized with A and B specific substances.[18]

Once the numbers of O and A_2 cells were estimated, calculation of the number of A_1 cells present was carried out according to the following equation:

$$\text{Number of } A_1 \text{ cells} = \text{total red cell count} - \text{number of O cells} - \text{number of } A_2 \text{ cells.}$$

It is obvious that the numbers of O, A_2 and A_1 cells present at any given time after transfusion can be only roughly estimated by these calculations. Nevertheless, counts made in quadruplicate every twenty-four to forty-eight hours yielded results which showed clearly the trend of cell destruction.

The numbers of autologous and total donated cells present at each point during the patient's hospital stay are shown in chart 2. The number of autologous cells ranged from 490,000 to 1,700,000. The latter figure was reached after the last

17. The A_2M cells were transfused a month prior to the patient's transfer. Because they were of the same type as the patient's, their destruction could only be assumed, but this seemed a fair assumption in view of subsequent observations. Destruction of the A_1M cells was demonstrated by the use of absorbed B serum.

18. Young, L. E., and Witebsky, E.: Studies of the Subgroups of Blood Groups A and AB: II. The Agglutinogen A_2; Its Detection with Potent B Serum and a Study of Its Inheritance, J. Immunol. **51**:111-116 (Aug.) 1945.

series of transfusions, and it coincided with a sharp drop in the proportion of the patient's cells which were reticulated.[19] This fact suggests that the transfusions affected the marrow in such a way that more mature (and less readily destroyed?) cells were released into the circulation. One might also argue that when large numbers of donated cells were in the patient's circulation fewer autologous cells were destroyed per unit of time, simply because there was some limit to the patient's total hemolytic capacity. At any rate, it is clear that both donated and autologous cells were destroyed by this patient at a rapid rate.

Chart 4 shows in more detail the picture of erythrocyte destruction during the first fifteen days following the large transfusion of O cells. It is apparent that both A_1 and O cells disappeared from the patient's circulation at a rapid rate and that the number of autologous cells showed a significant decline during this same period.

Reticulocytosis and Macrocytosis.—It is also noted (charts 2 and 3) that during the latter part of this period, when the total red cell count had fallen below

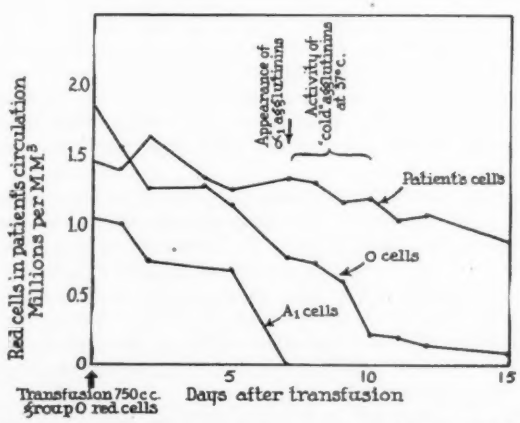

Chart 4 (case 1).—Disappearance of O, A_1 and autologous cells following last transfusion on April 20.

1,000,000, there was a sharp rise in the percentage of the patient's cells which were reticulated. On May 5 the total erythrocyte count was 880,000, of which 80,000 were O cells. The reticulocyte count on this date was 82 per cent, and it was calculated that approximately 90 per cent of the patient's own cells were reticulocytes. During the next month the patient made astonishing clinical improvement and the erythrocyte count rose to nearly 3,000,000 while the reticulocytes fell to 6 per cent. Thereafter, there was a slow but steady return to normal of the entire blood picture.

19. The proportion of the patient's cells which were reticulocytes was calculated by assuming that all reticulocytes present were autologous cells; for practical purposes this assumption was justified. The calculation was as follows:

$$\text{Per cent patient's cells reticulated} = \text{per cent total red cells reticulated} \times \frac{\text{total red cell count}}{\text{patient's red cell count}}.$$

It is evident in chart 3 that the decrease in reticulocytes during the period of recovery was closely parallel to the decrease in mean corpuscular volume of the erythrocytes. This striking parallelism suggests that the macrocytosis noted during the acute phase of the illness was due largely, if not entirely, to reticulocytosis. Dameshek and Schwartz [20] have referred to this type of macrocytosis as "pseudo" or "polychromatic" in contrast to the orthochromatic macrocytosis of untreated pernicious anemia.

Irregular Agglutinins in Case 1.—Alpha$_1$ (a_1) Agglutinins: Between March 1 and April 18 this patient (blood subgroup A_2) received a total of twenty-one transfusions from donors belonging to subgroup A_1. Alpha$_1$ ((a_1) agglutinins, active against A_1 cells at room temperature (chart 4), were first detectable on April 27 (titer 1:4). A maximal titer of 1:16 was reached on April 30, and this was followed by a gradual decline in potency (titer 1:4 on August 24; no agglutination of A_1 cells on October 31).

On several occasions it was possible to demonstrate activity of a_1 agglutinins at 37 C. in fresh serum from which the cold agglutinins had been removed, as described subsequently. In spite of this observation, it was believed that the rapid destruction of A_1 cells (chart 4) could not be attributed in any great measure to the action of a_1 agglutinins, because O cells, and probably autologous cells, were being destroyed at nearly the same rate during this period.

Cold Hemagglutinins: Throughout the entire period of observation of this patient (seven months) cold hemagglutinins were demonstrable in the serum in relatively constant amounts. The properties of these antibodies were studied in some detail.

Titrations were carried out by mixing 0.2 to 0.5 cc. of serum in serial twofold dilutions with equal volumes of 1 per cent suspensions of cells which had been washed three times with saline solution. The serum-cell mixtures were allowed to stand two hours at room and body temperatures and two or more hours at refrigerator temperature. They were then examined both grossly and microscopically for the presence or absence of agglutination. Titers were recorded in terms of the final dilution of serum after addition of the suspension of cells; that is, the first tube containing undiluted serum plus an equal volume of suspension of cells was recorded as diluted 1:2.

The method ordinarily used in this laboratory for titration of cold hemagglutinins is fully discussed in a separate paper.[21] During the study of case 1 the only noteworthy deviation from the usual technic was that of reading the end points microscopically instead of grossly. This was done by quickly transferring a drop of the serum-cell mixture to a plain glass slide for examination under the low power of a microscope. The microscopic readings were considered necessary in order to detect minor degrees of agglutination in absorption experiments. Agglutination graded 1 plus to 4 plus was visible grossly, while that graded plus-minus was detected only with the microscope.

Agglutinin-Absorption Studies: Although numerous agglutinin-absorption tests were performed, only one will be described in detail as a typical example. On June 6, 1944, 8 cc. of fresh defibrinated blood (hematocrit value 32 per cent) was placed in a large tightly stoppered test tube, which was then completely surrounded with cracked ice in a beaker. The beaker was placed in a refrigerator

20. Dameshek, W., and Schwartz, S. O.: Acute Hemolytic Anemia (Acquired Hemolytic Icterus, Acute Type), Medicine **19**:231-327 (May) 1940.

21. Young, L. E.: The Clinical Significance of Cold Hemagglutinins, Am. J. M. Sc. **211**:23-39 (Jan.) 1946.

at 4 C. for six hours. At the end of this period the tube was quickly packed in finely chipped ice in the carrier of a centrifuge and spun at 1,500 revolutions per minute for three minutes. The serum, from which the cold agglutinins had been largely absorbed, was then removed with a sterile drawn-out pipet and set aside for titration. Throughout the entire procedure, every effort was made to prevent warming of the tube.

After most of the serum had been removed, the cells were washed twice with equal volumes of isotonic solution of sodium chloride which had been chilled to 1 C. The cold agglutinins were then eluted from the cells by adding an amount of warm (37 C.) saline solution equal to that of the serum removed. After the mixture of cells and saline solution had stood at 37 C. for one hour, the tube was surrounded with warm (40 C.) water in the carrier of a centrifuge and spun at 2,000 revolutions per minute for ten minutes. The "eluate" containing the cold agglutinins was then removed with a sterile drawn-out pipet and set aside for titration.

Unabsorbed serum used in this and in other tests was separated from clotted (or defibrinated) blood by centrifugation at 2,000 revolutions per minute for ten minutes after incubation at 37 C. for one hour. This serum, the absorbed serum and the eluate were titrated with autologous A_1, A_2 and O cells on June 7, 1944. The tubes were examined after standing at room temperature for two hours and again after being warmed in a water bath at 37 C. for two hours. They were then placed in the refrigerator at 4 C. overnight and examined again on the following morning.

The results of this experiment are shown in table 1. The absorption of cold agglutinins has been described by a number of observers [22] but was of particular interest in this case because it served to separate the cold agglutinins from the α_1 agglutinins. It is clear from results with the absorbed serum that the cold agglutinins were largely removed while the α_1 agglutinins active against A_1 cells were relatively undisturbed. A prozone was noted when the absorbed serum was tested with autologous cells at 4 C. This was invariably observed in repeated experiments in which the patient's serum was absorbed with autologous and washed A_1, A_2 and O cells and then tested with autologous cells.

Thermal Amplitude of Agglutinins: Although the titer (1:32 to 1:64 with O cells and 1:64 to 1:128 with autologous cells) of cold agglutinins at 4 C. remained nearly constant throughout the period of study, the thermal amplitude of these antibodies fluctuated widely. Prior to April 27, 1944, no activity at room or body temperatures could be demonstrated. On that date, however, there was great difficulty in counting red cells because of slight agglutination, even when the diluting fluid was warmed to 37 C. It was also found that the patient's freshly drawn serum weakly agglutinated not only autologous cells but also other A_2 cells and A_1 and O cells at 37 C. and strongly agglutinated these cells at 22 C. Activity of these antibodies at body temperature persisted until May 1, 1944, after which date there was a gradual decline in activity at the warmer temperatures.

During the period April 27 to May 1 and thereafter serums that had been stored for periods of only one or two days agglutinated only A_1 cells at room temperature and showed no activity at 37 C. A table showing the titers against A_1, A_2 and O cells at refrigerator and at room temperature throughout the entire period of observation is presented in a separate paper.[1] Serum drawn on April 28

22. Stats, D., and Wasserman, L. R.: Cold Hemagglutination: An Interpretive Review, Medicine **22**:363-424 (Dec.) 1943.

and tested with B cells the following day gave titers of 1:128, 1:64 and 1:32 at 4, 24 and 37 C., respectively.

It is evident in table 1 that the eluate prepared on June 6, 1944, showed greater activity at warmer temperatures than did the serum from which it was prepared.

TABLE 1.—*Typical Results of Titration of Serum and Eluate with Various Cells at Refrigerator, Room and Body Temperatures: Separation of α_1 and Cold Agglutinins by Absorption, Case 1*

Serum or Eluate	Cells	Temp. of Test, C.	Degree of Agglutination Produced by Given Dilution of Serum or Eluate 1:2	1:4	1:8	1:16	1:32	1:64	1:128	
Serum drawn 6/6/44 unabsorbed	Autologous (A_2)	22	—	—	—	—	—	—	—	
		37	—	—	—	—	—	—	—	
		4	+++±	+++	+++	++	+	+	±	
	A_1	22	++	+	—	—	—	—	—	Agglutination of A_1 cells at 22 C. due to α_1 agglutinins
		37	—	—	—	—	—	—	—	
		4	+++±	+++	++	+±	+	±	—	
	A_2	22	—	—	—	—	—	—	—	Agglutination of all cells at 4 C. due to cold agglutinins
		37	—	—	—	—	—	—	—	
		4	+++	+++	++	+±	+	+	—	
	0	22	—	—	—	—	—	—	—	
		37	—	—	—	—	—	—	—	
		4	+++	+++	++	+±	+	±	—	
Serum drawn 6/6/44 absorbed with autologous cells	Autologous	22	—	—	—	—	—	—	—	Prozone with autologous cells
		37	—	—	—	—	—	—	—	
		4	±	±	+	+±	+	±	—	
	A_1	22	+	±	—	—	—	—	—	Minimal absorption of α_1 agglutinins
		37	—	—	—	—	—	—	—	
		4	+±	+	—	—	—	—	—	
	A_2	22	—	—	—	—	—	—	—	Marked absorption of cold agglutinins
		37	—	—	—	—	—	—	—	
		4	±	—	—	—	—	—	—	
	0	22	—	—	—	—	—	—	—	
		37	—	—	—	—	—	—	—	
		4	±	—	—	—	—	—	—	
Eulate 6/6/44 from autologous cells	Autologous	22	+	±	—	—	—	—	—	Greater activity of cold agglutinins in eluate at higher temperatures suggests release from inhibitory effect of serum
		37	+	—	—	—	—	—	—	
		4	++	++	++±	+	+	±	—	
	A_1	22	+	±	—	—	—	—	—	
		37	±	—	—	—	—	—	—	
		4	++	+±	+	+	±	—	—	
	A_2	22	+	±	—	—	—	—	—	
		37	+	—	—	—	—	—	—	
		4	++	+±	+	+	±	—	—	
	0	22	+	±	—	—	—	—	—	
		37	+	—	—	—	—	—	—	
		4	++	+±	+	+	±	—	—	

This phenomenon was noted in repeated experiments of similar type, in which fresh or one day old unabsorbed serum failed to agglutinate cells at room or body temperature while eluates prepared from the same serum showed weak but definite activity at these temperatures. This could not be demonstrated in eluates that had been stored in the refrigerator for more than a week or in eluates prepared from serum stored more than a few days.

These observations suggested that the patient's serum might contain some substance which inhibited activity of the cold agglutinins at warmer temperatures. This possibility was further explored by the following experiment: An eluate

prepared from fresh defibrinated blood on Aug. 24, 1944, by the same technic as that used with the specimen of June 6, was tested on August 25. The results were almost exactly like those shown in table 1. This eluate was tested again with autologous and A_1 cells on August 28. In each of four tubes was placed 0.2 cc. of eluate, to which 0.2 cc. of 1 per cent suspension of washed cells was added, as follows: to tube 1, autologous cells suspended in isotonic solution of sodium chloride; to tube 2, autologous cells suspended in absorbed serum[23]; to tube 3, A_1 cells suspended in saline solution, and to tube 4, A_1 cells suspended in absorbed serum.[23]

The tubes were examined after incubation at 37 C. for two hours and again after standing overnight at 22 C. They were then checked once more after a second incubation at 37 C. for two hours. The results are given in table 2 and indicate that the patient's serum had some inhibitory effect on agglutination. Similar results were obtained in three additional experiments of this type (also using A_2 and O cells), but when the cells were suspended in serum from normal persons the results were equivocal.

Determinations of thermal amplitude and absorptive characteristics of the patient's serum were made in duplicate with fresh, noninactivated serum and with serum heated at 56 C. for thirty minutes. The results were essentially the same.

The patient's serum drawn on Oct. 31, 1944 was absorbed with autologous and with O cells at 37 C. and then tested with autologous, A_1, A_2 and O cells at

TABLE 2.—*Inhibitory Effect of Serum on Agglutination at Warmer Temperatures, Case 1*

	Autologous Cells in		A_1 Cells in	
Temperature, C.	Saline Solution	Absorbed Serum	Saline Solution	Absorbed Serum
37	±	−	±	−
22	+	±	+	+
37	±	−	+	−

4, 22 and 37 C. The reactions indicated that neither antibodies nor inhibitory substances had been removed by "warm" absorption.

Attempts to define more completely the inhibitory property of the patient's serum were unsuccessful for three reasons: 1. It was impossible to obtain large quantities of serum and eluate. 2. Eluates deteriorated rapidly with storage. 3. Agglutination at the warmer temperatures was weak and often difficult to evaluate.

CASE 2.—M. G., a white woman, was 40 years of age when first admitted to the Strong Memorial Hospital, Oct. 3, 1929. She had had jaundice in association with a febrile illness at the age of 10 and had felt exhausted for several months in 1925 and 1927 but otherwise had been in good health until July 1929, when she began to suffer increasing fatigability, dizziness, numbness and tingling of the hands and anorexia. She had become pregnant in June 1929.

Family History.—The family history disclosed nothing of significance with respect to jaundice and anemia. Complete examinations of the blood of the patient's brother, sister and daughter failed to reveal any abnormalities. These examinations included study of wet preparations for the presence of spherocytes and tests of the fragility of the red cells in hypotonic saline solution.

23. The patient's serum was absorbed with autologous cells on August 24.

Physical Examination.—On the first admission the physical examination revealed normal vital signs. The patient was well developed and moderately obese. The skin and scleras were slightly icteric and the mucous membranes moderately pale. There was no glandular enlargement, and the liver and spleen were not palpable.

Laboratory Observations.—The red blood cell count was 2,960,000; white cell count 9,600, with a normal differential distribution, and hemoglobin value, 11.3 Gm. per hundred cubic centimeters. Reticulocytes varied from 8 to 16 per cent. There were moderate poikilocytosis and pronounced anisocytosis of the red cells; many of the larger cells showed basophilic stippling or polychromatophilia. Repeated tests of the fragility of the red cells in a hypotonic solution of sodium chloride were made by the customary method, with normal results. Platelets were present in normal numbers. The icterus index was 10. The only significant result of urinalysis was a strongly positive qualitative reaction for urobilin. There was no free hydrochloric acid in a fasting specimen of gastric contents. The patient could not retain the tube for additional examinations. Roentgenograms of the gastrointestinal tract and of the skull showed nothing abnormal. Wassermann and Kahn tests elicited negative reactions.

Course.—The patient was discharged from the hospital after completion of the aforementioned procedures but was later readmitted on four occasions for further study. Examinations of the blood were made on numerous visits to the hematologic laboratory. She gave birth to a normal girl by cesarean section on March 6, 1930, and a transfusion of 500 cc. of whole blood was given at that time without reaction.

Liver extract and iron were administered periodically from October 1929 until April 1932, without any beneficial effect. The patient's liver was first palpated with certainty in 1936 and the spleen in 1940; both organs have since remained 3 to 5 cm. below the costal margin. The red blood cell count gradually fell to a level of about 2,000,000 in 1942 and has remained near that figure. Since 1942 the hemoglobin has varied from 8.5 to 9.5 Gm. per hundred cubic centimeters, the hematocrit value from 28 to 29 per cent and the icterus index from 15 to 25. The white cells and platelets have remained normal. Prior to November 1942, the highest reticulocyte count recorded was 23 per cent, but since that date the counts have been consistently between 45 and 73 per cent (except after transfusions). The mean corpuscular volume of the red cells rose from a value of 118 when first determined, in 1939, to values of 135 to 150 during the period from 1942 to 1944. Spherocytes and nucleated red cells have never been observed in the peripheral blood, although numerous smears and wet preparations have been examined.

In 1942 and 1943 tests for the following reactions were carried out on three separate occasions with negative results: cold hemagglutination, warm and cold (Donath-Landsteiner) hemolysis, acid hemolysis (Ham) and sickling.

Since 1929 the patient has tired easily and has had frequent dizzy spells, but she managed to carry on work as a clerk, until June 9, 1944, when hospitalization was necessary because of cerebral thrombosis. She has since been in bed or in a chair most of the time. The transfusion experiments to be described were performed between the dates of June 12 and Nov. 13, 1944. The patient was in the hospital from June 9 to July 15 and from October 4 to 6, 1944. Splenectomy was contemplated on a number of occasions since 1929 but was not performed.

Fragility of Erythrocytes.—When tested by the customary method, the red cells of this patient appeared to have normal fragility in hypotonic solutions of sodium chloride. Repeated determinations were made in 1942, 1943, and on June 12, Oct. 17 and Nov. 13, 1944. On the last three dates tests were also carried out by the photoelectric technic previously described. By the latter method there appeared to

be a substantial increase in fragility in solutions with concentrations of salt between 0.40 and 0.64 per cent.

The mechanical fragility [24] of the cells of this patient was tested by a technic similar to that recently described by Shen, Castle and Fleming.[9] Blood was drawn into a mixture of potassium and ammonium oxalates and the hematocrit value adjusted to 40 per cent. A 1 cc. sample was then placed in a stoppered 125 cc. Erlenmayer flask containing 20 glass beads. The flask was attached to the periphery of a wheel 15 cm. in diameter and revolved at 24 revolutions per minute for two hours at room temperature. Samples were taken at one hour and two hours and the per cent of hemolysis determined.

The average figure for mechanical fragility was 5.3 per cent at one hour and 10.6 per cent at two hours for 15 normal, or nonanemic, controls. The patient's mechanical fragility was 18.8 per cent at one hour and 23.7 per cent at two hours on March 30, 1945 and 9 per cent and 22.6 per cent at one and two hours, respectively, on April 6, 1945. The normal values obtained were higher than those reported by Shen and associates, probably because of technical factors. Nevertheless, the fragility of the patient's cells to mechanical stress was much greater than that of any of the normal subjects tested.

It is possible that the apparently increased osmotic fragility of the patient's cells when tested by the colorimetric method was due to the trauma of centrifugation, since normal results were obtained by a method not involving centrifugation. This possibility is being investigated.

Transfusion Studies.—Survival of Transfused Normal Cells in Patient's Circulation: On June 12, 1944, 350 cc. of blood was removed from the patient, and the phlebotomy was immediately followed by a transfusion of 750 cc. of normal, fresh red cells given through the same needle.

The patient's blood group was OMNRh+. The blood group of all the three donors who contributed the normal cells was ONRh+. When anti-M serum was added to suspensions of the patient's cells after transfusion, the patient's own cells were agglutinated while the donated cells remained unagglutinated and could be counted in the usual way. By means of the technic previously described it was possible to determine the number of donated cells present in the patient's circulation at various intervals following the transfusion.

The results of this experiment are shown in chart 5, in which the gradual loss of donated cells over a period of more than one hundred days is evident. The number of autologous cells, calculated by subtracting the donor's cell count from the total red cell count, dropped to 1,690,000 after the phlebotomy and transfusion and then rose to a peak of 2,200,000 on the fourteenth day.

The proportion of the patient's own cells which were reticulocytes [19] declined rapidly during the first month after transfusion. There was also a sharp decrease in the excretion of fecal urobilinogen at this time.[25] These findings, together with the elevated count of autologous cells during this period, indicate that the transfusion had caused a decline in the rate of destruction of autologous cells and that more mature cells were being released from the marrow. Similar changes were described following transfusion in case 1 and were apparent to a lesser extent after the second transfusion in case 2 (to be described; see chart 5).

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24. The tests for mechanical fragility were carried out in the laboratory of Dr. Marion Emerson.

25. Difficulty was encountered in collection of feces from this patient. However, this difficulty was not sufficiently great to alter the interpretation of the results. Dr. Samuel H. Bassett and Miss Helen Schantz assisted in the determinations of the urobilinogen.

On Oct. 5, 1944, one hundred and fifteen days after the first phlebotomy and transfusion, 550 cc. of blood was removed from the patient. Immediately after this second phlebotomy, 500 cc. of normal red cells of group ONRh+ were transfused through the same needle. There was no untoward reaction after any of these procedures. Between October 5 and November 13 it was possible to check the patient's blood counts only four times. However, it was evident that the normal donated cells were again destroyed rather slowly and that transfusion had once more caused a decline in reticulocytes (figure 5).

Rapid Destruction of Patient's Cells After Transfusion to a Small Child: From the 550 cc. of citrated blood drawn from the patient on October 5, 150 cc. of red cells was obtained and transfused within two hours to a small child with probable aplastic anemia.[26] Seventy-three per cent of these cells were reticulocytes. As a result of the transfusion the child's reticulocyte count was raised by 17 per cent.

The child's blood group was A_2MNRh+, and since the cells from patient M. G. belonged to group OMNRh+ it was possible to follow the survival of the latter by using B serum. The results of this experiment are presented and discussed in

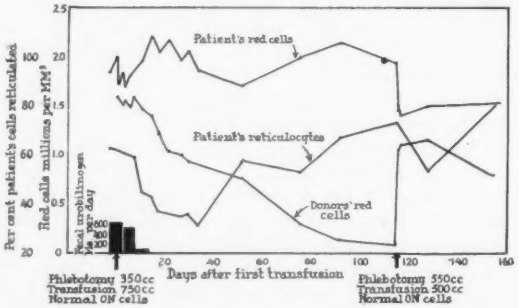

Chart 5 (case 2).—Hematologic changes during transfusion study.

detail in a separate paper.[2] It was found that the donated reticulocytes gradually matured in the child's circulation over a period of about six days and that all the transfused cells were destroyed in approximately eight days. It was demonstrated, however, that the reticulocytes were not destroyed until they had become mature. The child was later given two transfusions of normal cells, which were destroyed far more slowly.

Transfusion of Patient's Plasma to a Person Without Anemia: Within two hours after the 550 cc. of blood (containing 50 cc. of 5 per cent sodium citrate) was drawn from patient M. G. on October 5, 400 cc. plasma had been separated after centrifugation and frozen at — 35 C. The plasma was kept in the frozen state until October 18. At that time it was thawed at 37 C. and given intravenously to a man (blood group B) who was convalescing from cerebral thrombosis. The recipient's red blood cell count (average of four separate counts), hemoglobin content (average of two photoelectric determinations), hematocrit value (Wintrobe) and icterus index were checked daily for three days prior to the transfusion

26. The cells removed from the patient at the time of the first phlebotomy were also transfused to a small child, but it was necessary to discontinue this experiment for technical reasons.

of plasma and at two and twenty-one hours and every two days for ten days thereafter. No significant changes were produced by transfusion of 400 cc. of plasma which had been removed from the patient with hemolytic anemia.

COMMENT

Present State of Ignorance Regarding Hemolytic Anemias.—The hemolytic anemias have been classified by many writers and the various causes repeatedly enumerated.[27] They remain, however, among the least understood of all diseases encountered in the study of medicine.

For the sake of simplicity, the hemolytic disorders might be divided into two large groups: (1) those that are due to "extrinsic" agents and (2) those that are either congenital or due to "intrinsic" causes. It should be borne in mind that certain extrinsic agents, such as the malaria parasite, may initiate activity of hemolytic mechanisms that are apparently similar to or identical with those operating in cases due to purely intrinsic causes.[28] Moreover, sharp division of the group due to intrinsic causes into those that are congenital and those that are acquired is difficult, as will be discussed subsequently. The exact mode of action of various extrinsic agents, such as bacteria, parasites and chemicals, is not understood. However, the group due to intrinsic causes is even more mysterious, and it is this group which will be referred to for the most part in the subsequent discussion.

Much of the controversy relating to the group of intrinsic disorders is centered about one question. Are the patient's cells in any given case destroyed rapidly because they themselves are defective or because they are acted on by an abnormal destructive mechanism? The abnormal hemolytic processes operating in persons with intrinsic hemolytic disorders are of many types, but all of them are believed to involve aberrations of the reticuloendothelial system, particularly the spleen. The respective roles of various hemolysins and agglutinins, presumably produced by the reticuloendothelial system and perhaps by lymphoid tissue, and of erythrostasis in the spleen have been discussed at length by Dameshek,[29] Ham and Castle [30] and others.[31]

27. (*a*) Pepper, O. H. P.: A Survey of the So-Called Hemolytic Anemias, Ann. Int. Med. **12**:796-810 (Dec.) 1938. (*b*) Haden, R. L.: The Nature of Hemolytic Anemia, in A Symposium on the Blood and Blood-Forming Organs, Madison, Wis., University of Wisconsin Press, 1939. (*c*) Davis, L. J.: Haemolytic Anaemias, Edinburgh M. J. **50**:589-616, 1943. (*d*) Dameshek and Schwartz.[20]

28. Foy, H.; Kondi, A.; Rebelo, A., and Soeiro, A.: Survival of Transfused Red Cells in Blackwater Fever Circulation and of Blackwater Red Cells in Normal Circulation, Tr. Roy. Soc. Trop. Med. & Hyg. **38**:271-286 (March) 1945.

29. Dameshek, W.: (*a*) Hemolytic Syndromes: A Five Year Progress Report, Bull. New England M. Center **5**:74-79 (April) 1943; (*b*) Medical Progress: Hematology, New England J. Med. **230**:514-521 (April 27); 542-550 (May 4)

(Footnote continued on next page)

Significance of Spherocytes.—The controversy just referred to involves particularly cases in which spherocytes are present. These cells were formerly regarded solely as products of defective erythropoiesis and were considered pathognomonic of congenital hemolytic jaundice. The term "spherocytic jaundice" was therefore applied to this disease entity.[32] More recently, however, these cells have been described in cases of hemolytic disorders labeled "acquired" or "atypical."[33] Moreover, spherocytosis and increased osmotic fragility have been observed in normal cells after exposure to agents such as hemolytic serums,[20] lysolecithin [31c] and heat.[34]

Dameshek [29c] has stated that he regards all spherocytes as cells which have been injured after delivery from the bone marrow. He postulates the injurious action of specific hemolysins not only in "acquired" hemolytic anemias but also in congenital hemolytic jaundice and in nocturnal hemoglobinuria. This view is held in spite of the fact that hemolysins have been demonstrated in vitro in only a few cases of the "acquired" and in no cases of the other types of hemolytic anemia —and in spite of the fact that circulating hemolysins have been demonstrated in the absence of spherocytes.[35]

1944; (*c*) Medical Progress: Hematology, ibid. **232**:250-255 (March 1); 280-286 (March 8) 1945.

30. Ham, T. H., and Castle, W. B.: Studies on Destruction of Red Blood Cells: Relation of Increased Hypotonic Fragility and of Erythrostasis to the Mechanism of Hemolysis in Certain Anemias, Proc. Am. Philos. Soc. **82**:411-419 (May 20) 1940; Relation of Increased Hypotonic Fragility and of Erythrostasis to the Mechanism of Hemolysis in Certain Anemias, Tr. A. Am. Physicians **55**:127-132, 1940.

31. (*a*) Doan, C. A.; Wiseman, B. K., and Erf, L. A.: Studies in Hemolytic Jaundice, Ohio State M. J. **30**:493-504 (Aug. 1) 1934. (*b*) Sharpe, J. C., and Tollman, J. P.: Refractory Hemolytic Anemia: A Report of Five Cases in Which Treatment Was with Splenectomy, Arch. Int. Med. **70**:11-32 (July) 1942. (*c*) Dameshek, W., and Miller, E. B.: Pathogenetic Mechanisms in Hemolytic Anemias, ibid. **72**:1-17 (July) 1943. (*d*) Dameshek and Schwartz.[20]

32. Krumbhaar, E. B.: Modern Concepts of Anemia from the Clinical Standpoint, Bull. New York Acad. Med. **13**:501-511 (Sept.) 1937.

33. (*a*) Watson, C. J., and Clarke, W. O.: Hemolytic Anemia, Staff Meet., Bull. Hosp. Univ. Minnesota **12**:356-370 (April 4) 1941. (*b*) Mason, V. R.: Acquired Hemolytic Anemia, Arch. Int. Med. **72**:471-493 (Oct.) 1943. (*c*) Dameshek and Schwartz.[20] (*d*) Dameshek.[29]

34. Shen, S. C.; Ham, T. H., and Fleming, E. M.: Studies on Destruction of Red Blood Cells: III. Mechanism and Complications of Hemoglobinuria in Patients with Thermal Burns; Spherocytosis and Increased Osmotic Fragility of Red Blood Cells, New England J. Med. **229**:701-713 (Nov. 4) 1943.

35. Farrar, G. E., Jr.; Burnett, W. E., and Steigman, A. J.: Hemolysinic Anemia and Hepatic Degeneration Cured by Splenectomy, Am. J. M. Sc. **200**: 164-172 (Aug.) 1940.

Reference has already been made to the studies of Dacie and Mollison,[4] who found that cells from a patient with congenital hemolytic jaundice, taken both before and after splenectomy, disappeared rapidly after transfusion into normal recipients. Normal cells, on the other hand, survived normally when transfused into patients with this disorder. These observations have been interpreted by Dacie and Mollison and by Davis [27c] as indicating that defective formation of erythrocytes is the basic abnormality in congenital hemolytic jaundice. Dameshek,[29b] however, stated that these experiments do not exclude the role of hemolysins because "spherocytes, already being . . . on the road to hemolysis, are more quickly destroyed in the intact spleen" of a normal recipient. Dacie and Mollison admitted the possibility that the hemolytic agent postulated by Dameshek (although not demonstrated in vitro) might be specific for the patient's own cells and would thus permit normal donated cells to survive normally.

In cases of congenital hemolytic jaundice there is obvious need of more transfusion experiments of the type reported by Dacie and Mollison. It is also essential that these studies be accompanied by careful search for autohemolysins and isohemolysins. This need is more urgent in view of the fact that some investigators [36] have described cases of congenital hemolytic jaundice in which transfused normal cells may have been destroyed rapidly.

Differentiation of Congenital and Acquired or Atypical Hemolytic Jaundice.—Diagnosis is relatively easy in cases of typical congenital hemolytic jaundice. However, differentiation from the heterogeneous group of cases of "acquired" or atypical hemolytic jaundice may often be very difficult, as pointed out by numerous observers.[37] The late Lord Dawson of Penn [36a] expressed the opinion that the "defects themselves are inborn," and he doubted the existence of acquired forms of hemolytic anemia. Doan and associates [31a] likewise expressed the belief that "hemolytic icterus is a disease, usually, if not always, congenital." On

36. (*a*) Dawson, B. E.: The Hume Lectures on Haemolytic Icterus, Brit. M. J. **1**:921-928 (May 30) 1931: (*b*) Lowe, R. C.: A Study of Hemoglobin Metabolism and Hematology in a Case of Congenital Hemolytic Jaundice During Clinical Crisis, Repeated Transfusions and Before and After Splenectomy, Am. J. M. Sc. **206**:347-352 (Sept.) 1943.

37. (*a*) Davidson, L. S. P.: Macrocytic Haemolytic Anaemia, Quart. J. Med. **25**:543-578 (Oct.) 1932. (*b*) Josephs, H. W.: Studies in Haemolytic Anemia: I. Haemolysis, Compensatory Regeneration and Erythroblastosis, Bull. Johns Hopkins Hosp. **62**:25-52 (Jan.) 1938. (*c*) Rastetter, J. W., and Murphy, F. D.: Acquired Hemolytic Jaundice, Am. J. Digest. Dis. & Nutrition **4**:805-810 (Feb.) 1938. (*d*) Sutton, H. B., and Moore, N. S.: The Diagnosis and Treatment of Congenital Hemolytic (Spherocytic) Jaundice: Report of a Case with Unusual Blood Findings Altered by Liver Therapy, Ann. Int. Med. **21**:698-708 (Oct.) 1944. (*e*) Davis.[27c] (*f*) Doan, Wiseman and Erf.[31a] (*g*) Mason.[33b]

the contrary, Dameshek [29b] has more recently stated that most hemolytic anemias are not hereditary. Davis,[27c] in 1943, reviewed a group of 47 cases of subacute and chronic idiopathic hemolytic anemia and concluded that most of these cases differed fundamentally from congenital hemolytic jaundice. Microspherocytosis with increased osmotic fragility of the red cells was recorded in only 4 of the 47 cases. The response to splenectomy was variable in contrast to the uniformly favorable results in cases of the more familiar disorder.

Thompson [38] has studied three family groups in which hemolytic anemia was present in various generations but in which spherocytes (and leptocytes) were lacking. Because of this report and because of ignorance concerning the nature of acquired hemolytic anemias it is probably wise to apply the term "atypical" to this heterogeneous group as suggested by Thompson. Accordingly, both cases described in this paper have been labeled "atypical" rather than "acquired."

Use of Transfusions in the Study of Hemolytic Anemias.—Of Intrinsic Origin: It is clear that present knowledge of the hemolytic disorders is decidedly limited. Even in the case of congenital hemolytic jaundice, which is perhaps the best known of the hemolytic diseases, there are many questions which remain unanswered. The atypical cases are the subject of even more debate and speculation. Much of the difficulty encountered in studying the hemolytic anemias can be attributed to the fact that in vivo processes often cannot be duplicated in the test tube. It is therefore logical that attention should be directed to the usefulness of transfusion experiments, which are the only means available for studying in vivo the fate of certain cells.

In case 1 of the present report there was no opportunity to determine the manner of disappearance of the patient's cells after transfusion into a normal recipient. However, normal cells were rapidly destroyed in the patient's circulation, and it is considered likely that their destruction was initiated by cold agglutinins (and possibly a_1 agglutinins) of high thermal amplitude. In accordance with the views of Stats and Wasserman [22] and Dameshek,[29c] it is suggested that a small degree of intravascular agglutination of both autologous and donated cells rendered the erythrocytes highly susceptible to destruction. Complete destruction of the agglutinated cells may have been brought about by the mechanical trauma of circulation or by more specific activity of the reticuloendothelial system or by both. The fact that rapid destruction of cells continued for some time after splenectomy suggests that the spleen may not have been responsible. Neither autohemolysins nor isohemolysins could be

38. Thompson, W. P.: Hemolytic Jaundice, Bull. New York Acad. Med. **15:** 177-187 (March) 1939.

demonstrated, but it is possible that their presence was masked by the irregular agglutinins [20] or by some type of blocking antibody.[39]

At any rate, it is fair to suspect that in this case the fundamental abnormality was not in the process of red cell formation but rather in the mechanism of red cell destruction. Anatomically speaking, it was primarily not in the erythron but in the reticuloendothelial system—that is, the tissue responsible for production of irregular agglutinins and for the breakdown (particularly in the spleen) of both normal and agglutinated or damaged cells.

In case 2 the patient's cells were rapidly destroyed in her own body and after transfusion to a child who destroyed normal cells at a much slower rate. Normal cells donated to this patient disappeared slowly in a linear fashion. Moreover, 400 cc. of the patient's plasma, which contained no irregular antibodies demonstrable in vitro, did not have a measurable hemolytic effect on the cells of a normal recipient. It seems likely, therefore, that the fundamental defect in this case was in the erythron, that is, the erythroid cells of the bone marrow and the erythrocytes themselves.

Some authorities might argue that in the second case the red cells were not defective "at birth" but were damaged "postnatally" by hemolysins after delivery from the marrow. They would argue further that hemolysins were present even though they could not be demonstrated in vitro. They would contend still further that the hemolysins were specific for the patient's own cells and therefore allowed normal donated cells to be destroyed slowly by normal processes. There is little to be gained by dogmatically denying the existence of such hemolysins. However, it seems fair to state that the burden of proof rests on the authors who assert that they do exist and that they are largely responsible for the rapid and indiscriminate destruction of erythrocytes in most of the intrinsic cases, both congenital and atypical. Before this controversy can be settled, much more must be learned concerning the exact manner and site of formation of antibodies,[40] the role of lymphocytes in this process [41] and the nature of blocking antibodies.[39]

39. Wiener, A. S.: A New Test (Blocking Test) for Rh Sensitization, Proc. Soc. Exper. Biol. & Med. **56**:173-176 (June) 1944. Fisk, R. T., and Morrow, P.: The Occurrence of Anti-Rh Blocking Antibodies in Anti-Rh Serums, ibid. **58**: 72-73 (Jan.) 1945. Diamond, L. K., and Abelson, N. M.: The Demonstration of Anti-Rh Agglutinins: An Accurate and Rapid Slide Test, J. Lab. & Clin. Med. **30**:204-212 (March) 1945. Levine, P., and Gilmore, E. L.: The First Stage of Antigen-Antibody Reaction in Infectious Mononucleosis, Science **101**:411-412 (April 20) 1945.

40. Burnet, F. F.; Freeman, M.; Jackson, A. V., and Bush, D.: The Production of Antibodies, Melbourne, Australia, Macmillan & Co., Ltd., 1941.

41. Kass, E. H.: The Occurrence of Normal Serum Gamma-Globulin in Human Lymphocytes, Science **101**:337-338 (March 30) 1945.

Transfusion experiments of the type described deserve much wider use in the study of hemolytic anemias. More extensive application of this in vivo test will provide valuable information concerning its usefulness and limitations. It would be of interest to transfuse into normal recipients (or into patients with anemia due to loss of blood) erythrocytes from patients with sickle cell anemia, sickle cell trait and target cell–oval cell syndromes. Additional experiments with cells from patients with nocturnal hemoglobinuria will also be worth while. In cases of chronic hemolytic anemia of only moderate severity, it is considered safe to remove several hundred cubic centimeters of the patient's blood, provided the phlebotomy is followed immediately by a transfusion of normal whole blood or red cells. In fact, patients may benefit temporarily from this procedure, inasmuch as they receive normal cells in exchange for defective cells.

Transfusion of normal erythrocytes into patients with almost any type of hemolytic anemia, either extrinsic or intrinsic in type, would yield information of value provided the pattern of disappearance of the cells can be determined by means of differential agglutination tests. Observations on the effect of transfusion of serum or plasma from patients with hemolytic disorders into normal recipients would also be of interest. It is believed, however, that the latter type of experiment will seldom be justified in view of the possible risk to the recipient. In any case, certain possibilities must be kept in mind in interpreting the results of such experiments, namely (1) specificity of hemolysins for the patient's own cells, (2) complete binding of hemolysins by the patient's cells so that none may be present in separated plasma and (3) absorption of transfused hemolysins by the recipient's erythrocytes or tissue cells or both in such a way that hemolysis does not occur. In addition, the quantity of plasma transfused must obviously be taken into account.

It is reasonable at this point to speculate on the manner in which transfusion experiments might aid in classifying the various hemolytic diseases. On the basis of such experiments, it might be possible to divide intrinsic hemolytic anemias into two large groups, as shown in table 3.

It must be emphasized that this classification is largely conjectural, and much more work will be necessary before it can have meaning. Furthermore, it is likely that the division into groups A and B will not be clearcut—that is, it may be found that patients in group A destroy normal donated cells rapidly during acute phases of their illness. Some of the studies already reported suggest that this may be the case. It may also be found that cells taken from patients in group B, once they have been damaged or in some way acted on by agglutinins or hemol-

ysins, are rapidly destroyed after transfusion into normal recipients. It is believed, however, that in spite of obvious limitations transfusion experiments will be of distinct value in exploring the intrinsic hemolytic anemias. They might also throw light on the mechanisms involved in some of the cases of hemolytic anemia of extrinsic origin, caused by burns, chemicals and infectious agents.

Of Extrinsic Origin: The value of this type of study in investigation of the extrinsic group is shown by the recent report of Foy and associates.[28] It was found that cells from a patient with active blackwater fever

TABLE 3.—*Conjectural Classification of Intrinsic Hemolytic Anemias on the Basis of Transfusion Experiments*

Group	Manner of Destruction of Patient's Cells After Transfusion into Normal Recipient	Manner of Destruction of Normal Donated Cells After Transfusion into Patient	Effect of Patient's Serum or Plasma on Cells of Normal Recipient	Suspected Site of Hemolytic Abnormality	Clinical Diagnoses
A	Rapid, at least partially exponential	Normal, linear (or variable during acute phases ?)	Probably little or none	Erythron	Congenital hemolytic jaundice; sickle cell anemia; thalassemia; nocturnal hemoglobinuria; certain chronic atypical forms (such as case 2)
B	No experiments on which to base opinion	Rapid, chiefly exponential	No experiments on which to base opinion	Reticuloendothelial system (including spleen) and its products (antibodies)	Acute atypical hemolytic anemia; certain chronic atypical forms (such as case 1); some cases associated with malignant growths, disseminated lupus erythematosus, etc.; cold hemoglobinuria (syphilitic); hemolytic disease of newborn *

* Hemolytic disease of the newborn, or erythroblastosis fetalis, is included here for the sake of completeness. It differs from the other hemolytic disorders listed in that antibodies are formed in the mother and passively transferred to the child.

survived only six days after transfusion into a normal recipient. The survival time of normal cells transfused into patients with blackwater fever nine days after active hemolysis had ceased was thirty to thirty-five days. Eighteen months later the survival time of donated cells was normal. According to the authors, these results indicated the presence of a factor capable of destroying all cells and once cells of persons with blackwater fever were acted on by this factor they were readily destroyed even in a normal circulation. It was found, however, that 500 cc. of plasma from a patient with active blackwater fever transfused into a patient with an acute attack of malaria failed to cause hemolysis in the recipient. It was concluded that either insufficient plasma was used in this experiment or any hemolysins present had been "used up" by the blackwater cells.

This interesting report from Foy's laboratory serves to illustrate three important points: (1) that transfusion experiments are useful in studying hemolytic anemia of extrinsic origin; (2) that extrinsic factors may initiate the activity of mechanisms similar to, or identical with, those operating in purely intrinsic cases and (3) that cells, other than spherocytes, which have been damaged by hemolysins are rapidly destroyed, even in a normal circulation. If it is found that these results apply to some of the anemias of purely intrinsic origin and if the cells of some of the patients with intrinsic hemolytic anemias of group B are found to be destroyed normally in normal circulations, it will be necessary to add a group C to the classification shown in table 3. Included in group C would be the diseases of patients whose cells are rapidly destroyed in normal circulations and who themselves destroy normal cells rapidly.

Cold Hemagglutinins in Hemolytic Anemia: Since Widal's [42] initial observations in 1908, the presence of cold hemagglutinins in the serum of patients with hemolytic anemia has been noted by many observers,[43] but in only 3 previously reported cases has activity of these antibodies been demonstrable at body temperature.[44] As a general rule, the thermal amplitude of cold agglutinins is proportional to the titer,[22] activity at body temperature being expected only when the titer is extremely high at temperatures near 0 C. Case 1, in which the titer at 4 C. was not

42. Widal, F.; Abrami, P., and Brulé, M.: Autoagglutination des hématies dans l'ictère hémolytique acquis, Compt. rend. Soc. de biol. **64**:655-657, 1908.

43. (*a*) Watson, C. J.: Hemolytic Jaundice and Macrocytic Hemolytic Anemia: Certain Observations in a Series of Thirty-Five Cases, Ann. Int. Med. **12**:1782-1796 (May) 1939. (*b*) Antopol, W.; Applebaum, I., and Goldman, L.: Two Cases of Acute Hemolytic Anemia with Auto-Agglutination Following Sulfanilamide Therapy, J. A. M. A. **113**:488-489 (Aug. 5) 1939. (*c*) Reisner, E. H., and Kalkstein, M.: Auto-Hemolysinic Anemia with Autoagglutination: Improvement After Splenectomy, Am. J. M. Sc. **203**:313-322 (March) 1942. (*d*) Rothstein, I., and Cohn, S.: Acute Hemolytic Anemia, Autoagglutination, Toxic Hepatitis and Renal Damage Following Sulfathiazole Therapy, Ann. Int. Med. **16**:152-162 (Jan.) 1942. (*e*) Dameshek, W.: Cold Agglutinins in Acute Hemolytic Reactions, J. A. M. A. **123**:77-80 (Sept. 11) 1943. (*f*) Layne, J. A., and Schemm, F. R.: Acute Macrocytic Hemolytic Anemia Occurring Following Administration of Sulfadiazine, J. Lab. & Clin. Med. **29**:347-351 (April) 1944. (*g*) Köpplin, F.: Autohämagglutination und Anämie, Ztschr. f. klin. Med. **130**:784-788, 1936. (*h*) Dameshek.[13] (*i*) Dameshek and Schwartz.[20] (*j*) Mason.[33b]

44. (*a*) Wiener, A. S.: Hemolytic Transfusion Reactions: I. Diagnosis, with Special Reference to the Method of Differential Agglutination, Am. J. Clin. Path. **12**:189-199 (April) 1942. (*b*) Kracke, R. R., and Hoffman, B. J.: Chronic Hemolytic Anemia with Autoagglutination and Hyperglobulinemia: Report of a Fatal Case, Ann. Int. Med. **19**:673-684 (Oct.) 1943. (*c*) Evans, R. S.: Acute Hemolytic Anemia with Autoagglutination: A Case Report, Stanford M. Bull. **1**:178-182 (Aug.) 1943.

remarkable, is therefore one of the few notable exceptions to this general rule and serves to emphasize that thermal amplitude may be a "constitutional characteristic." [22]

Widal and associates [42] expressed the opinion that cold agglutinins might serve to distinguish acquired hemolytic anemia from the congenital type, but it has since been found that these agglutinins are present in significant titer in relatively few cases.[45] Moreover, they have been described by Masters and associates [46] and by Young [21] in cases that conformed in every respect to the congenital type.

The role of cold hemagglutinins in the process of rapid destruction of erythrocytes has been the subject of considerable debate. In some instances the cold agglutinins have persisted in undiminished titer after the hemolytic process has subsided and even after splenectomy, as in case 1 of this report. In addition, it has been emphasized that hemolytic anemias have been described which were identical in every respect except for the presence of cold agglutinins in some and the absence of same in others. After summarizing the available evidence, Stats and Wasserman [22] concluded that these antibodies were the result rather than the cause of hemolytic anemia.

Wiener,[44a] on the contrary, after describing a case in which autoagglutinins were active at body temperature, expressed the opinion that they had played a part in the destruction of the patient's erythrocytes in vivo. This conclusion appears reasonable so far as it applies to cases in which the agglutinins have extremely high thermal amplitude. However, complete understanding of the role of cold hemagglutinins in hemolytic disorders must await further observation, with particular emphasis on the mechanical fragility of weakly agglutinated erythrocytes.

The relation of cold agglutinins to splenomegaly and their disappearance following splenectomy in some cases and persistence in others have been discussed elsewhere.[21]

Multiple Evidence of Abnormal Antibody Production: It was pointed out in a separate paper [1] that in 3 of the 5 reported cases of development of a_1 or a_2 agglutinins following transfusion the patients were suffering from atypical hemolytic anemia. It was further emphasized that in 2 of these cases, other irregular antibodies were present in addition to the a_1 and a_2 antibodies. Kracke and Hoffman [44b] have recently described a case of chronic atypical hemolytic anemia in which the patient's serum contained (1) autoagglutinins active at body temperature, (2) antibodies producing positive reactions to Wassermann,

45. Stats and Wasserman.[22] Watson.[43a]

46. Masters, J. M.; Zerfas, L. G., and Mettel, H. B.: Congenital Hemolytic Icterus: Treatment with Splenectomy; Reports of Two Cases, Am. J. Dis. Child. 37:1254-1259 (June) 1929.

Kahn, Kline and Eagle tests on repeated occasions and (3) globulin in a concentration of 5.36 Gm. per hundred cubic centimeters. The serologic reactions for syphilis became negative within two weeks after splenectomy.

All these observations point to abnormal activity of the reticuloendothelial system as a common denominator in certain persons in whom atypical hemolytic anemia is liable to develop. It appears as though this remarkable tissue (and perhaps the lymphoid tissue [41]) for no apparent reason sometimes produces sports of various types and that only one of the various sports produced may be responsible for rapid destruction of red cells. Whether or not this phenomenal activity is dependent on a fundamental constitutional abnormality is not clear.

Inhibitory Properties of Serum: In case 1 it was repeatedly observed that cold hemagglutinins had greater thermal amplitude after being separated in saline eludates from the whole serum. This fact indicated that the serum had an inhibitory property, the exact nature of which could not be determined because of several practical difficulties.

Josephs [47] demonstrated in normal human plasma a substance which reduced the rate of blood destruction in sickle cell anemia and in congenital hemolytic jaundice. It was suggested that the function of this substance was to aid in maintaining the normal equilibrium between formation and destruction of erythrocytes and that a lack of this substance might be responsible for certain hemolytic phenomena.

Maegraith, Findlay and Martin [48] found that washed tissues (lung, liver, kidney, spleen, bone marrow and muscle) lysed saline suspensions of red cells of the same species (man, monkey and guinea pig). Lysis was inhibited by addition of serum to the tissue–red cell mixture. The lytic agent, which was thought to be an enzyme, appeared to be species specific, while the serum inhibitor was not. These investigators postulated that the degree of hemolysis occurring at any time in a given animal might depend on the balance of inhibitor over lytic enzyme activity. They further suggested that some hemolytic disorders might be due either to interference with the activity of the inhibitor or to its actual destruction.

Farrar, Burnett and Steigman [35] demonstrated the presence of a hemolysin in a case of atypical hemolytic anemia and found that it was neutralized by normal homologous serum. Ecker, Castro and Seifter [49]

47. Josephs, H. W.: Studies in Haemolytic Anemia: II. The Presence of an Anti-Haemolytic Factor in Human Plasma, Bull. Johns Hopkins Hosp. **62**:53-69 (Jan.) 1938.

48. Maegraith, B.; Findlay, G. M., and Martin, N. H.: Mechanism of Lysis of Red Blood Cells, Nature, London **151**:252 (Feb. 27) 1943.

isolated from human serum a protein fraction which inhibited certain serologic reactions. Whether or not this substance is related to or identical with the inhibitory substances referred to by other investigators remains to be seen. It is clear, however, that the possible function of serum inhibitors in maintaining the erythrocyte formation-destruction balance cannot be overlooked. Moreover, it may be found that some hemolytic disorders, particularly those of group B, are due to the absence or inactivation of inhibitors rather than to the presence of irregular hemolysins or agglutinins.

The beneficial effect of transfusions in hemolytic anemia has been noted by many observers. A single transfusion has sometimes been apparently curative or has at least resulted in improvement beyond that attributable to the quantity of red cells given.[20] Beard [50] has recently emphasized the value of plasma transfusions and has reported uniformly good results from daily administration of large quantities. In view of the probable existence of inhibitory substances in plasma and the high incidence of reactions following transfusions of whole blood, the rationale of plasma therapy in hemolytic anemia is evident.

Value of Splenectomy: The wisdom of performing splenectomy in cases of congenital hemolytic jaundice has long been established. The results of this operation in atypical cases, however, have been highly irregular.[51] One cannot be certain that splenectomy alone was responsible for the apparent cure in case 1 of this report, nor can one predict what might be accomplished by this procedure in case 2. In cases of acute illness there is relatively little time for detailed studies, but in the cases of the more chronic types it is obviously desirable to make extensive investigations prior to and following operation. Information accumulated in this way may make it possible for the physician in the future more judiciously to select certain atypical cases for splenectomy.

Initiation of Hemolytic Activity: The nature of the stimulus which initiates rapid destruction of erythrocytes in intrinsic cases is not understood. Numerous hypotheses have been offered, but none is entirely satisfactory. Does the patient suddenly become sensitized to his own erythrocytes and thus develop autoagglutinins or autohemolysins [52]? Is there destruction, inactivation or deficiency of inhibitory substances which ordinarily hold lytic factors in balance [53]? Does the phagocytic

49. Ecker, E. E.; Castro, G. L., and Seifter, S.: Isolation from Fresh Human Serum of a Fraction Which Inhibits Certain Serological Reactions, Proc. Soc. Exper. Biol. & Med. **58**:95-96 (Jan.) 1945.

50. Beard, M. F.: Hemolytic Anemia, South. M. J. **37**:448-450 (Aug.) 1944.

51. Lawrence, J. S.: Indications for Splenectomy in a Medical Practice, Internat. Clin. **2**:221-238 (June) 1937. Dameshek.[13] Davis.[27c] Thompson.[38]

52. Wiener, A. S.: Macrocytic Anemia of Pregnancy, J. A. M. A. **125**:990 (Aug. 5) 1944. Dameshek and Schwartz.[20] Dameshek.[29c]

53. Masters, Zerfas and Mettel.[46] Josephs.[47]

activity of the spleen and other parts of the reticuloendothelial system suddenly get out of hand—and if so, why? These and many other questions remain unanswered. The patient who at age 1 or age 60 suddenly or gradually begins to destroy his own cells at a rapid rate furnishes food for speculation. Reflection on this puzzle makes one appreciate that even the normal mechanism of red cell destruction is not understood.

The observations recorded in this paper represent an attempt to clarify the factors operating in 2 unusual examples of hemolytic disease. They do not, however, provide a solution of even one of the many problems presented by this mysterious group of disorders. Further struggle with these problems is needed, and it can be expected to produce valuable results because "the disease hemolytic anemia has an interest beyond itself." [36a]

SUMMARY

Clinical and laboratory observations on 2 cases of chronic atypical hemolytic anemia are presented in detail.

The important features of case 1 were (*a*) rapid destruction of all transfused red cells received from 30 donors, (*b*) presence of cold hemagglutinins which became slightly active at body temperature, (*c*) development of a_1 agglutinins following twenty-one transfusions of A_1 blood, and (*d*) apparent cure following splenectomy in spite of the persistence of cold hemagglutinins.

In case 2 phlebotomy was performed twice and followed immediately, each time, by transfusion of normal erythrocytes. The patient's red cells were rapidly destroyed after transfusion to a small child, but the patient's plasma had no hemolytic effect on the cells of a normal recipient. Donated normal cells survived normally in the patient's circulation.

The usefulness of transfusion experiments in the study of hemolytic anemias is emphasized. It is suggested that on the basis of such experiments it may be possible to divide the intrinsic hemolytic disorders into 2 groups: A, in which the primary defect is in the red cell itself, and B, in which the primary abnormality is in the hemolytic mechanism.

The behavior of cold hemagglutinins and a_1 agglutinins in case 1 is described. In view of the high thermal amplitude of these antibodies, their role in blood destruction cannot be minimized.

The significance of an inhibitory substance in the serum of case 1 and in normal serum or plasma is discussed in relation to the rationale of plasma therapy in hemolytic anemia.

Miss Helen Zimmerman and Miss Leah Schwendler gave technical assistance in this study.

ABSORPTION, DISTRIBUTION AND EXCRETION OF STREPTOMYCIN

JOHN D. ADCOCK, M.D.
AND
ROBERT A. HETTIG, M.D.
ANN ARBOR, MICH.

STREPTOMYCIN, an antibiotic substance obtained from the micro-organism Actinomyces griseus, was described in January 1944 by Schatz, Bugie and Waksman.[1] This material was shown to possess activity in vitro over a wide range of bacteria but was of particular interest because it was effective against many bacteria which were not susceptible to the chemotherapeutic substances then available for the treatment of human infections. Subsequent reports have confirmed these observations and, in addition, have shown that streptomycin is effective in the treatment of experimental infections with organisms of the Eberthella and Salmonella groups [2] and with Pseudomonas aeruginosa, Shigella gallinarum, Brucella abortus and Proteus vulgaris,[3] as well as with Pasteurella tularensis [4] and with the Klebsiella organisms.[5] Streptomycin was also found to possess activity against the tubercle bacillus both in vitro [6] and in vivo.[7] The toxicity of a partially purified product for mice was reported to be of a fairly low order.[2]

From the Department of Internal Medicine, University Hospital, University of Michigan.

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1. Schatz, A.; Bugie, E., and Waksman, S. A.: Streptomycin, a Substance Exhibiting Antibiotic Activity Against Gram-Positive and Gram-Negative Bacteria, Proc. Soc. Exper. Biol. & Med. **55**:66, 1944.

2. Robinson, H. J.; Smith, D. G., and Graessle, O. E.: Chemotherapeutic Properties of Streptomycin, Proc. Soc. Exper. Biol. & Med. **57**:226, 1944.

3. Jones, D.; Metzger, H. J.; Schatz, A., and Waksman, S. A.: Control of Gram-Negative Bacteria in Experimental Animals by Streptomycin, Science **100**:103, 1944.

4. Heilman, F. R.: Streptomycin in the Treatment of Experimental Tularemia, Proc. Staff Meet., Mayo Clin. **19**:553, 1944.

5. Heilman, F. R.: Streptomycin in the Treatment of Experimental Infections with Micro-Organisms of the Friedländer Group (Klebsiella), Proc. Staff Meet., Mayo Clin. **20**:33, 1945.

(Footnotes continued on next page)

As is the case with penicillin, streptomycin is at present measured by reference to its antibiotic activity. The unit of streptomycin has been defined as that amount of the material which completely inhibits the growth of a strain of Escherichia coli in 1 cc. of nutrient broth. Recently a method has been described for the preparation of crystalline streptomycin hydrochloride,[8] which is reported to have an activity of 800 units per milligram. The present unit would then be equivalent to 0.00125 mg. of the crystalline material.[8a]

Within the past year streptomycin has become available in sufficient quantity for limited trial against human infections. One report has appeared regarding its use in typhoid,[9] and in this report the toxicity of the material was considered to be compatible with clinical use.

The present studies were undertaken to determine the absorption, distribution and excretion of streptomycin when given by various routes and to provide an understanding of the problems of administration of the drug.

METHODS AND MATERIALS

The concentration of streptomycin in various body fluids was determined by a method recently described by Stebbins and Robinson,[10] with minor modifications. The technic of this test is as follows: The test organism, known as Staphylococcus aureus S. M.,[11] is grown in nutrient broth for sixteen hours at 37 C. A 10^{-4} dilution of this culture is made into the melted test agar[12] at a temperature of 45 C. After thorough mixing, the test agar is pipetted into sterile Petri dishes in 10 cc. quantities and allowed to solidify. Beveled porcelain cylinders are heated, and the beveled end is placed on the surface of the agar, forming a seal between the cylinder and the agar as cooling occurs. The cylinders are then

6. Schatz, A., and Waksman, S. A.: Effect of Streptomycin and Other Antibiotic Substances upon Mycobacterium Tuberculosis and Related Organisms, Proc. Soc. Exper. Biol. & Med. **57**:244, 1944.

7. Feldman, W. H., and Hinshaw, H. C.: Effects of Streptomycin on Experimental Tuberculosis in Guinea Pigs: A Preliminary Report, Proc. Staff Meet., Mayo Clin. **19**:593, 1944.

8. Kuehl, F. A.; Peck, R. L.; Walti, A., and Falkers, K.: Streptomyces Antibiotics: I. Crystalline Salts of Streptomycin and Streptothricin, Science **102**: 34, 1945.

8a. Shortly after the preparation of this manuscript it was proposed that amounts of streptomycin be expressed as equivalents of streptomycin base. Under this plan 1 unit represents 1 microgram of pure streptomycin base and 1,000,000 units represents 1 Gm. It is expected that this plan will be generally adopted.

9. Reimann, H. A.; Elias, W. F., and Price, A. H.: Streptomycin for Typhoid: A Pharmacologic Study, J. A. M. A. **128**:175 (May 19) 1945.

10. Stebbins, R. B., and Robinson, H. J.: A Method for Determination of Streptomycin in Body Fluids, Proc. Soc. Exper. Biol. & Med. **59**:255, 1945.

11. Obtained from the Merck Institute for Therapeutic Research.

12. Bacto peptone 1 per cent, Bacto beef extract 0.4 per cent, salt 0.25 per cent, agar 1.5 per cent. The p_H is adjusted to 7.5 with sodium hydroxide.

filled with fluids containing streptomycin and the Petri dishes incubated for sixteen to eighteen hours at 30 C. Well defined zones of inhibition of growth are then apparent around the cylinders. The diameters of these zones are proportional to the concentration of streptomycin in the specimen and are measured to the nearest 0.5 mm. To minimize the error, each specimen is run in triplicate, different Petri dishes being used and the diameters of the three zones of inhibition averaged.

To determine the concentration of streptomycin in unknown specimens, it is necessary to construct a standard curve of reference for each day's determinations. In the case of serum, this is accomplished by adding streptomycin to pooled normal serum in concentrations of 1, 2, 4, 8, 12, 16 and 20 units per cubic centimeter and handling the individual specimens as described previously. The diameters of the zones of inhibition are plotted against the known concentrations of strepto-

TABLE 1.—*Results of Assays Run on Normal Serum to Which Streptomycin Had Been Added*

Amount of Streptomycin Added to Normal Serum, Units per Cc.	Results of Assays, Units per Cc.					
	1	2	3	4	5	6
40	42.0	37.5	40.0	37.5	50.0	48.7
30	33.0	33.0	27.0	27.5	32.5	31.2
22	19.0	18.7	26.2			
14	14.0	11.2	13.0	13.5	10.5	14.1
6	6.2	5.8	5.5			

TABLE 2.—*Results of Assays Run on Normal Urine to Which Streptomycin Had Been Added*

Amount of Streptomycin Added to Normal Urine, Units per Cc.	Results of Assays, Units per Cc.					
	1	2	3	4	5	6
2,000	2,100	1,740	1,700	1,420	2,000	
1,000	1,000	1,070	850	940	1,000	1,000
500	475	500	500	495	550	
100	86	120	95	95	110	90
50	43	52.5	43.5	60		
10	8	8.5				

mycin. The concentration of streptomycin in the unknown serum may then be computed by reference to this curve. Unknown serums are diluted with pooled normal serums when necessary to insure a reading which will fall within the limits of the standard curve. The concentrations in pleural and abdominal fluids, spinal fluids and bile have likewise been determined by reference to this curve. In determining the concentration of streptomycin in urine, the most consistent results have been obtained by substituting tenth-molar phosphate buffer solution at p_H 7.4 for serum in making up the standard curve and by diluting the unknown urine with this buffer.

In order to determine the reliability of this method, streptomycin was added to pooled normal serum in various concentrations, and assays were run on each specimen on several occasions. The results are shown in table 1. In table 2 are shown the results of similar experiments when streptomycin was added to normal urine in amounts covering the usual range encountered in patients receiving the material. An analysis of these rather small samples shows that for serum the mean percentage error is $+ 0.43 \pm 2.9$ per cent (standard deviation 11.22)

TABLE 3.—*Data on Absorption, Distribution and Excretion of Streptomycin*
Twenty-five experiments on twenty-one subjects

Subject					Streptomycin		Serum			Urine					Other Body Fluids	
							Time,†							% of Dose Excreted,		
No.	Sex	Age	Weight, Lb.	Diagnosis	Dose, Units	Route	Hr.	Min.	Units per Cc.	Time, Hr.	Volume, Cc.	Units per Cc.	Units Excreted	Cumulative	Hr.	Units per Cc.
1	M	15	119	Urinary tract infection	50,000	Intravenously	..	5	6.5	1	125	55	6,875	13		
							..	15	6.5	2	200	27.5	5,500	24		
							..	30	3.75	3	54	12	648	26		
							1	..	2.5	4	127	16	2,032	30		
							2	..	1.7	6	160	12	1,920	34		
							3	..	1.5							
							4	..	1.2							
							6	..	Trace							
2	F	20	119	Pulmonary tuberculosis	100,000	Intravenously	..	4	16.0	2	158	325	51,350	51		
							..	30	10.0	4	90	140	12,600	64		
							1	..	7.2	10	300	40	12,000	75		
							1	30	4.5							
							2	..	3.3							
							3	..	2.7							
							4		2.3							
							8	..	1.0							
							10	..	Trace							
3	M	21	210	Pulmonary tuberculosis	200,000	Intravenously	..	5	20.0	2	400	162.5	65,000	32		
							..	30	14.0	4	177	200	35,400	50		
							1	..	9.0	12	1,165	32	37,280	68		
							1	30	7.0	24	400	32	12,800	75		
							2	..	6.0							
							4	..	3.8							
							8	..	2.0							
							10	..	1.2							
							12	..	1.0							
4	M	24	171	Pulmonary tuberculosis	200,000	Intravenously	..	9	25.0	2	900	87.5	78,750	39		
							..	30	15.0	4	850	37.5	31,875	55		
							1	..	8.7	12	1,405	25	35,125	72		
							1	30	7.5	24	300	Trace				
							2	..	7.0							
							4	..	3.5							
							8	..	1.7							
							10	..	Trace							

† Times are from the end of administration of streptomycin.

5	M	25	168	Normal subject	500,000	Intravenously	..	5	52.5	2	220	600	132,000	26
							..	30	41.0	6	215	425	91,375	44
							1	..	25.5	12	270	300	81,000	61
							1	30	21.0					
							2	..	13.0					
							3	..	10.5					
							4	..	7.0					
							8	..	3.5					
							10	..	2.2					
							12	..	1.5					
6	M	54	143	Pulmonary tuberculosis	200,000	Subcutaneously	..	30	10.5	2	138	125	17,250	8
							1	..	10.0	4	168	235	39,480	28
							2	..	8.0	12	285	95	27,075	41
							4	..	4.5	24	332	50	16,600	50
							8	..	2.2					
							10	..	1.4					
							12	..	1.1					
7	M	61	162	Tuberculous adenitis	200,000	Subcutaneously	..	30	7.0	2	300	252	75,600	37
							1	..	7.0	4	122	207	25,254	50
							1	30	8.0	12	314	95	29,830	65
							2	..	7.5	24	400	35	14,000	72
							4	..	4.0					
							8	..	1.7					
							10	..	1.5					
							12	..	1.0					
7	M	61	162	Tuberculous adenitis	200,000	Subcutaneously	..	30	6.3	2	170	215	36,550	18
							1	..	8.0	4	200	185	37,000	36
							1	30	8.5	12	610	60	36,600	55
							2	..	8.0	22½	550	33	18,150	64
							4	..	5.7					
							8	..	2.0					
							10	..	1.5					
							12	..	1.0					
8	F	21	107	Pulmonary tuberculosis	100,000	Intramuscularly	..	30	5.5	2	245	100	24,500	24
							1	..	6.0	4	225	60	13,500	38
							1	30	5.5	10	600	43	25,800	63
							2	..	5.5	24	345	9.4	3,243	67
							3	..	4.5					
							4	..	3.0					
							8	..	1.0					
							10	..	Trace					
9	F	25	99	Pulmonary tuberculosis	100,000	Intramuscularly	1	..	5.7	24	670	125	83,750	83
							2	..	3.5					
							6	..	1.25					
							10	..	Trace					

TABLE 3.—*Data on Absorption, Distribution and Excretion of Streptomycin—(Continued)*

Subject					Streptomycin		Serum			Urine					Other Body Fluids	
							Time,†							% of Dose Excreted,		
No.	Sex	Age	Weight, Lb.	Diagnosis	Dose, Units	Route	Hr.	Min.	Units per Cc.	Time, Hr.	Volume, Cc.	Units per Cc.	Units Excreted	Cumulative	Hr.	Units per Cc.
10	M	25	156	Pulmonary tuberculosis	200,000	Intramuscularly	..	30	10.0	2	775	75	57,125	28		
							1	..	11.0	4	440	43	18,920	38		
							1	30	13.0	12	1,470	40	58,800	67		
							2	..	8.0	24	300	18	5,400	70		
							4	..	4.0							
							8	..	2.4							
							10	..	1.2							
							12	..	Trace							
10	M	25	156	Pulmonary tuberculosis	200,000	Intramuscularly	..	30	10.5	2	825	70	57,750	28		
							1	..	12.0	4	200	61	12,200	35		
							1	30	12.0	12	1,500	40	60,000	65		
							2	..	12.0	22½	690	7	4,800	67		
							4	..	6.3							
							8	..	1.2							
							10	..	1.0							
							12	..	Trace							
11	M	27	142	Pulmonary tuberculosis	200,000	Intramuscularly	..	30	11.5	2	410	162	66,625	33		
							1	..	12.5	4	400	130	52,000	59		
							1	30	12.5	12	800	68	54,400	86		
							2	..	9.0	24	284	32	9,088	91		
							4	..	4.8							
							8	..	Trace							
							12	..	0							
12	M	11	54	Cardiospasm	200,000	Intramuscularly	..	30	22.5	2	35	1,500	52,500	26		
							1	..	22.5	4	36	1,000	36,000	44		
							2	..	17.5	12	110	350	38,500	63		
							4	..	9.0	24	237	42	9,954	68		
							8	..	3.0							
							12	..	Trace							
13	M	37	157	Pulmonary tuberculosis	500,000	Intramuscularly	..	5	2.2	2	184	800	147,200	29		
							..	30	9.0	4	350	250	87,500	47		
							1	..	18.0	12	300	550	165,000	80		
							2	..	17.0	24	286	62	17,732	83		
							4	..	7.5							
							8	..	4.2							
							10	..	3.4							
							12	..	1.0							(Pleural)

14	M	16	94	Constrictive pericarditis; pleural and abdominal effusion	500,000	Intramuscularly	..	30	27.5	2	73	1,800	131,400	26	1	Trace
							1	..	32.5	4	53	1,600	84,800	43	2	2.6
							1	30	25.0	12	228	500	114,000	66	4	3.0
							2	..	20.0	24	227	72	16,344	69	6	4.0
							4	..	12.0						10	5.5
							6	..	8.5						(Ascitic)	
							10	..	3.0						2	8.5
							12	..	1.8						4	11.5
															10	5.0
															(Pleural)	
15	F	49	95	Pulmonary neoplasm; pleural effusion	500,000	Intramuscularly	..	30	30.0	2	190	575	109,250	22	2	6.0
							1	..	32.5	4	115	375	43,125	30	4	9.5
							2	..	26.0						8	12.0
							3	..	20.0						12	7.0
							4	..	18.0							
							8	..	6.5							
							12	..	4.0							
															(Bile)	
16	M	42	108	Postoperative common duct obstruction; T tube in common duct; jaundiced	500,000	Intramuscularly	..	5	8.5	2	250	350	87,500	17	1	0
							1	..	30.5	5½	190	650	123,500	42	2	4.2
							1	30	21.0	12	510	100	51,000	52	3	7.0
							2	..	20.0						4	5.7
							3	..	12.0						6	5.5
							4	..	7.0						8	3.0
							8	..	3.0						10	1.7
							10	..	1.5						12	Trace
							12	..	Trace							
17	M	26	172	Normal subject	500,000	Intramuscularly	..	5	2.5	2	185	550	101,750	20		
							..	30	16.0	4	60	1,050	63,000	33		
							1	..	17.0	8	260	450	117,000	56		
							1	30	18.0	12	245	225	55,125	67		
							2	..	16.0							
							3	..	12.0							
							4	..	10.0							
							8	..	4.5							
							10	..	3.5							
							12	..	2.5							

TABLE 3.—*Data on Absorption, Distribution and Excretion of Streptomycin—(Continued)*

Subject					Streptomycin		Serum			Urine					Other Body Fluids	
							Time,†							% of Dose Excreted,		
No.	Sex	Age	Weight, Lb.	Diagnosis	Dose, Units	Route	Hr.	Min.	Units per Cc.	Time, Hr.	Volume, Cc.	Units per Cc.	Units Excreted	Cumulative	Hr.	Units per Cc.
18	F	32	129	Postoperative common duct stricture; T tube in common duct; not jaundiced	500,000	Intramuscularly	..	5	2.5	4½	370	700	259,000	51	(Bile)	
							..	30	34.0	7½	200	100	20,000	55	2	8.0
							1	..	26.0	12	635	75	49,625	65	4	10.0
							1	30	26.0						6	8.0
							2	..	19.0						8	4.2
							3	..	13.0						12	Trace
							4	..	8.0							
							8	..	3.5							
							12	..	Trace							
19	F	20	130	Pulmonary tuberculosis	100,000	Inhalation	..	30	0	2	160	0				
							1	..	0	8	160	0				
							2	..	0							
							3	..	0							
4	M	24	171	Pulmonary tuberculosis	200,000	Inhalation	..	5	0	6	720	3.5	2,520	1		
							..	30	0							
							1	..	0							
							2	..	Faint trace							
							6	..	0							
20	M	46	167	Hypopituitarism	400,000	Mouth	..	30	0	2	210	0				
							1	..	0	6	305	0				
							2	..	0	11	520	Trace				
							4	..	0	30	993	Trace				
							7	..	0							
							9	..	0							
							11	..	0							
21	F	59	124	Salmonella carrier	400,000	Mouth	1	..	0	24	...	0				
							2	..	0							
							3	..	0							
							6	..	0							
							9	..	0							
4	M	24	171	Pulmonary tuberculosis	500,000	Mouth	..	30	0	6	1,000	0				
							1	..	0							
							2	..	0							
							3	..	0							
							6	..	0							

and for urine the mean percentage error is -3.3 ± 2.1 per cent (standard deviation 11.15).

The subjects studied included ward patients and a few normal volunteers. There was no clinical evidence of impaired renal function in any one of these persons. Blood specimens were drawn from the antecubital veins and were, in most instances, allowed to clot, the serum being separated by centrifugation. In a few instances the blood was defibrinated with glass beads and the serum and cells handled separately. Urine was collected as voided specimens. All specimens were stored at approximately 5 C. until the determinations of streptomycin content could be run. In most instances the tests were made within forty-eight hours of collection, but occasionally a longer period of storage elapsed.

Streptomycin [13] was dissolved in sterile, pyrogen-free distilled water or 0.85 per cent sodium chloride solution in concentrations of 25,000, 50,000 and 100,000 units per cubic centimeter for single doses given intramuscularly or subcutaneously. The dose was dissolved in 10 or 20 cc. of 0.85 per cent saline solution when given as a single intravenous injection. For continuous intravenous or subcutaneous infusions the material was dissolved in either 0.85 per cent solution of sodium chloride or in 5 per cent dextrose solution in a concentration of 1,000 units per cubic centimeter. When given orally, the dose was placed in 200 cc. of tap water. Two patients received the material by inhalation of the nebulized material. The dose, dissolved in 4 cc. of water, was placed in a DeVilbiss no. 40 nebulizer, and the open end of the nebulizer was held just inside the lips, with the mouth open. Rubber tubing connected the nebulizer to a tank supplying oxygen at a flow of 6 liters per minute. A Y tube was placed in the tubing from the oxygen tank to the nebulizer so that the flow could be diverted during the expiratory phase of respiration. It required from forty to fifty minutes to complete the administration of the 4 cc. of solution.

OBSERVATIONS

Absorption and Excretion of Streptomycin Given by Various Routes.—This portion of the study was devoted largely to a consideration of the absorption and excretion of single doses of streptomycin. Serum levels were determined at intervals up to twelve hours following administration of the dose. Specimens of urine were collected whenever possible at two hours and four hours after giving streptomycin. The urine from four hours to twelve hours was pooled into a single specimen, as was the urine from twelve hours to twenty-four hours. Table 3 gives the data obtained in 25 experiments on 21 subjects who were given single doses of streptomycin.

In every instance in which a subject was given streptomycin parenterally it was possible to demonstrate the presence of the material in the serum. When the dose was 200,000 units or more, demonstrable amounts remained in the serum for twelve hours in virtually all subjects. As had been anticipated, the initial concentration in the serum

13. The streptomycin used in these studies was supplied by Merck & Co., Inc. The material was partially purified, the active principle being present as the hydrochloride.

was considerably higher after intravenous than after intramuscular injection. Chart 1 shows the serum levels and the cumulative excretion in the urine when 100,000 units was given intravenously to 1 subject

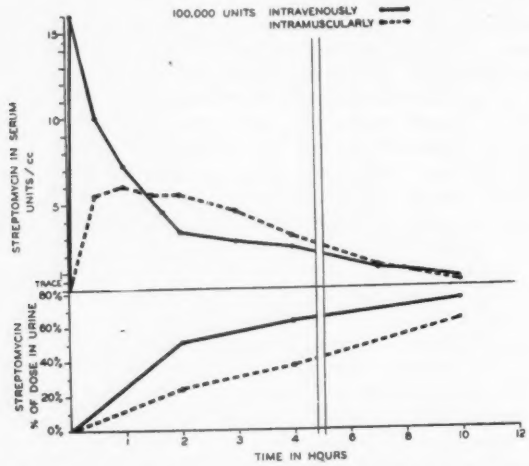

Chart 1.—Concentrations of streptomycin in the serum and the rate of urinary excretion following administration of 100,000 units intravenously (subject 2, table 3) and intramuscularly (subject 8, table 3).

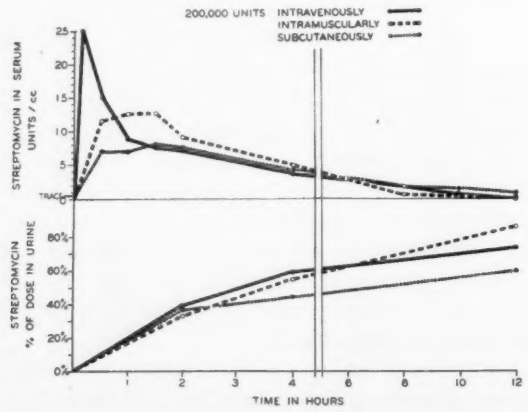

Chart 2.—Concentrations of streptomycin in the serum and the rate of urinary excretion following administration of 200,000 units intravenously (subject 4, table 3), intramuscularly (subject 11, table 3) and subcutaneously (subject 7, table 3).

and intramuscularly to another subject of approximately the same age and weight. Chart 2 gives the same data following the injection of 200,000 units intravenously, intramuscularly and subcutaneously for 3

subjects. In spite of significant initial differences, the serum levels were approximately the same at the end of two hours regardless of the route of administration. The peak levels in the serum were roughly proportional to the amount administered. This is illustrated in chart 3.

The rate of urinary excretion was greatest during the first two hours of observation at the time of highest serum levels. On the average, a larger percentage of the dose was excreted in the first two hours after intravenous than after intramuscular or subcutaneous dosage, but there was considerable overlap in individual cases. For the patients receiving streptomycin parenterally, the total excretion in twelve hours varied from 41 to 86 per cent of the dose, with a mean of 65 per cent. The

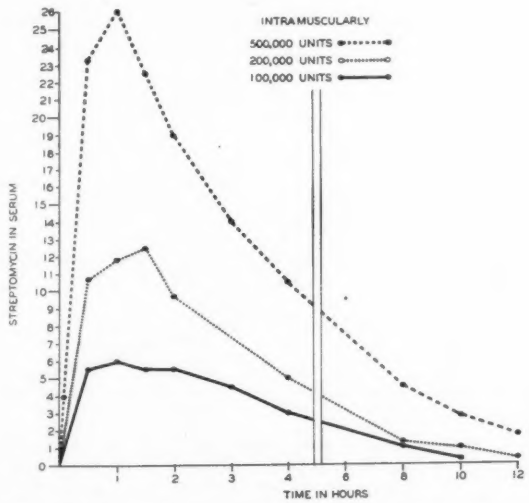

Chart 3.—Concentrations of streptomycin in the serum following varying doses given intramuscularly: 100,000 units to 1 subject, 200,000 units to 3 subjects (composite curve) and 500,000 units to 6 subjects (composite curve).

urine excreted between twelve and twenty-four hours after the injection usually contained only small additional amounts, varying from traces to 9 per cent of the dose.

The excretion of streptomycin in bile was studied on 2 patients who had undergone operation for obstruction of the common duct and had T tube remaining in the common duct (subjects 16 and 18, table 3). One patient (subject 16) was jaundiced; the other was not. Both received 500,000 units intramuscularly, and blood and urine were collected in the usual manner. Bile was collected by means of the T tubes. Chart 4 shows the levels in serum and bile at intervals during the twelve hours of study for subject 18. Unfortunately, it was impossi-

ble to be certain that the collection of bile was quantitative for either subject; hence calculation of the total excretion in the bile could not be made.

The oral administration of streptomycin in single doses of 400,000 and 500,000 units was not followed by any demonstrable serum level, and traces or none at all appeared in the urine. To 1 patient (subject 21, table 3) streptomycin was later given orally for six days in a dosage of 4,000,000 units per day (500,000 units every three hours). On this schedule, traces were noted in the serum in daily determinations and between 0.2 and 0.5 per cent of each day's dose was present in the twenty-four hour pooled specimens of urine. A stool obtained after three days on this dosage contained 8,700 units per gram of wet stool. The inhalation of streptomycin also failed to give rise to any appreciable level in the serum, and only small amounts appeared in the urine.

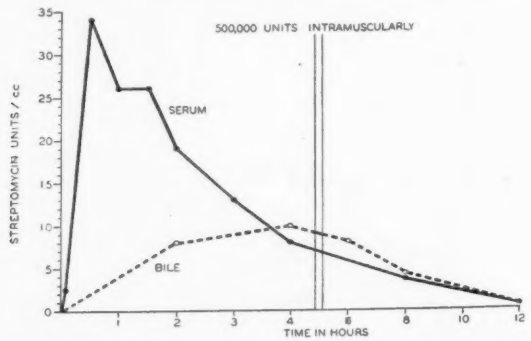

Chart 4.—Concentrations of streptomycin in the serum and in the bile following administration of 500,000 units intramuscularly (subject 18, table 3).

Distribution of Streptomycin.—Chart 5 shows the concentrations of streptomycin in serum, pleural fluid and ascitic fluid in a patient with constrictive pericarditis who received 500,000 units intramuscularly. Chart 6 shows the results of a similar experiment on a patient with a pulmonary neoplasm and an accompanying pleural effusion. In both subjects the level in the aberrant fluid rose as the serum levels fell and eventually exceeded the level in the serum.

On 2 subjects, blood was defibrinated and tests were run on serum and cells separately. There was no streptomycin demonstrable in the cells which had been hemolyzed by freezing, and the level in the serum obtained by this method was, within the limits of error of the method, the same as that in serum obtained by allowing the blood to clot.

A small number of data were collected regarding the diffusion of streptomycin into the spinal fluid. The subjects had received strepto-

mycin by repeated intramuscular injection or by continuous subcutaneous infusion for a period of twenty-four hours or longer. Specimens of blood and of spinal fluid were obtained as nearly simultaneously as

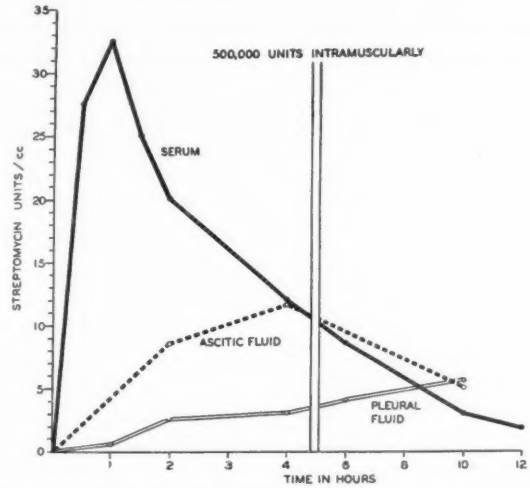

Chart 5.—Concentrations of streptomycin in serum, pleural fluid and ascitic fluid following administration of 500,000 units intramuscularly (subject 14, table 3).

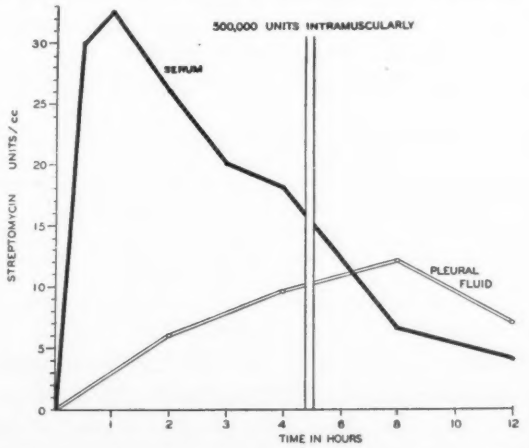

Chart 6.—Concentrations of streptomycin in serum and pleural fluid following administration of 500,000 units intramuscularly (subject 15, table 3).

possible and were taken at a time judged to represent the low point in serum concentration for the particular dosage schedule employed. The results of these determinations for 4 patients without clinical evidence of

meningitis and for 3 patients with definite meningitis are listed in table 4.

Two patients with tuberculous meningitis received streptomycin by continuous subcutaneous infusion in excess of forty-eight hours and extending to the time of death. Postmortem examinations were done within six hours after death, affording an opportunity to study the distri-

TABLE 4.—*Streptomycin in Serum and Spinal Fluid Taken Simultaneously*

Patient No.	Diagnosis	Streptomycin in Serum, Units/Cc.	Streptomycin in Spinal Fluid, Units/Cc.
1	Salmonella carrier	4.0	Trace
2	Pulmonary tuberculosis	6.5	Trace
3	Infection of urinary tract	25.0	2.0
4	Infection of urinary tract	12.0	Trace
5	Tuberculous meningitis	35.0	13.7
		17.5	12.0
		17.5	11.2
6	Tuberculous meningitis	45.0	18.5
7	Hemophilus influenzae meningitis	16.0	4.5
		15.7	4.0
		17.5	12.5
		10.5	4.5

bution of streptomycin in the organs. Postmortem serum was obtained for purposes of comparison, and gallbladder bile was collected in 1 case. Weighed samples of the organs were ground with sand and a measured amount of isotonic solution of sodium chloride. The resultant mixtures were allowed to stand eighteen hours at refrigerator temperature, after which they were centrifuged and the supernatant fluid assayed. Table 5

TABLE 5.—*Distribution of Streptomycin in Body Fluids and Tissues Obtained Post Mortem*

Patient No.	Serum, Units per Cc.	Gallbladder Bile, Units per Cc.	Kidney, Units per Gm.	Lung, Units per Gm.	Heart Muscle, Units per Gm.	Brain, Units per Gm.	Liver, Units per Gm.
1	12	21	20	6	1	0	0
2	43	..	93	6	5	Trace	Trace

gives the results of assays with the concentrations in serum and bile expressed as units per cubic centimeter and in the organs as units per gram.

The Renal Excretion of Streptomycin.—The rate of urinary excretion of streptomycin is appreciably slower than that reported for penicillin,[14] a substance which has a similar origin and might be expected

14. Rammelkamp, C. H., and Keefer, C. S.: The Absorption, Excretion and Distribution of Penicillin, J. Clin. Investigation **22**:425, 1943.

to have a similar behavior. This difference is well illustrated in chart 7, which shows the serum levels and the rate of excretion in urine for both substances given intravenously. The subjects were young females of approximately the same height and weight. Penicillin determinations were done by a modification [15] of the Rammelkamp procedure.[16]

These sharp differences prompted the following experiments on the urinary excretion of streptomycin.

Two normal male subjects of average height and weight, without evidence of impaired renal function, were catheterized and given streptomycin by continuous intravenous infusion at carefully controlled rates for periods of two hours. The first ninety minutes of each period was allowed for the stabilization of plasma levels, and the urine was discarded. During the last thirty minutes of each

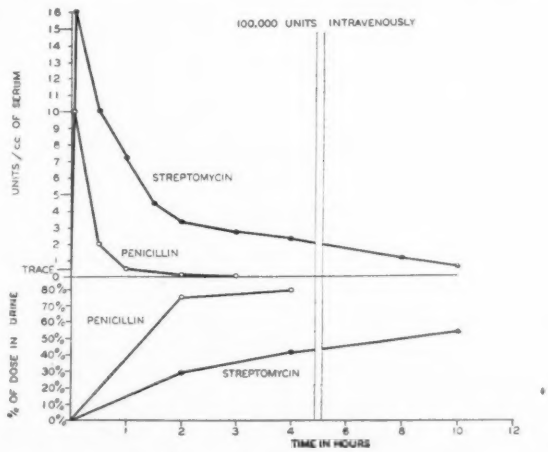

Chart 7.—Serum concentrations and rate of urinary excretion of streptomycin (1 subject) and penicillin (1 subject) following administration of 100,000 units intravenously.

period, a timed urine specimen was collected and a blood specimen was drawn. Immediately after the completion of the first test period, the rate of infusion was doubled and the experiment was repeated in the same fashion. Determinations of the streptomycin content of the samples were made on the day of collection.

The results of assay on these specimens, together with calculations of the plasma clearance values, are presented in table 6. From 38 to 67 cc. of plasma was cleared of streptomycin per minute, which is well

15. Kirby, W. M. M., and Rantz, L. A.: Methods of Measuring Penicillin Concentrations in Body Fluids, J. Bact. **48**:603, 1944.

16. Rammelkamp, C. H.: A Method for Determining the Concentration of Penicillin in Body Fluids and Exudates, Proc. Soc. Exper. Biol & Med. **51**:95, 1942.

within the 130 cc. per minute that might be expected of glomerular filtration alone.[17] This adequately explains the observed differences in rate of excretion of streptomycin and penicillin, since it has been shown by Rantz and Kirby[18] that the plasma clearance values for penicillin are in the range of 750 to 1,120 cc. per minute. There is also other indirect evidence[19] that penicillin is excreted by the tubules in addition to glomerular filtration.

TABLE 6.—*Urinary Excretion of Streptomycin During Continuous Intravenous Infusion*

Subject	Thirty Minute Test Period*	Infusion Rate, Units per Hour	Urine Volume, Cc.	Urine Excretion, Cc. per Min.	Concentration of Streptomycin		Plasma Cleared of Streptomycin, Cc. per Min.
					Urine, Units per Cc.	Plasma, Units per Cc.	
A	1	50,000	32.5	1.08	500	14	38
	2	100,000	48	1.60	800	19	67
B	1	125,000	122	4.66	187.5	13.5	64
	2	250,000	57	1.9	800	25	60

* Each thirty minute test period was preceded by a period of one and one-half hours during which the rate of infusion was the same as that of the test period.

COMMENT

The results reported here are in essential agreement with those of Reimann and his colleagues.[20] The parenteral administration of streptomycin gave rise to serum levels which were roughly proportional to the amount injected. On the other hand, oral dosage failed to give rise to any appreciable level in the serum. The high concentration of streptomycin in the stool after oral administration indicates poor absorption rather than massive destruction or inactivation within the gastrointestinal tract.

After parenteral injection, from 41 to 86 per cent of the dose appeared in the urine during the first twelve hours with very small additional amounts thereafter. This suggests that some of the material

17. Smith, H. W.; Goldring, W., and Chasis, H.: The Measurement of the Tubular Excretory Mass, Effective Blood Flow and Filtration Rate in the Normal Human Kidney, J. Clin. Investigation **17**:263, 1938.

18. Rantz, L. A., and Kirby, W. M. M.: The Absorption and Excretion of Penicillin Following Continuous Intravenous and Subcutaneous Administration, J. Clin. Investigation **23**:789, 1944.

19. Rammelkamp, C. H.: Excretion of Penicillin in Man, Proc. Soc. Exper. Biol. & Med. **53**:30, 1943. Beyer, K. H.; Woodward, R.; Peters, L.; Verwey, W. F., and Mattis, P. H.: The Prolongation of Penicillin Retention in the Body by Means of Paraaminohippuric Acid, Science **100**:107, 1944.

20. Elias, W. F., and Durso, J.: Blood, Urine and Fecal Levels of Streptomycin in the Treatment of Human Infections of E. Typhosa, Science **101**:859, 1945. Reimann, Elias and Price.[9]

may be destroyed or inactivated within the body or in the urine itself. It seems unlikely that the amounts of streptomycin appearing in the bile could account for the discrepancy between the dosage and the urinary excretion.

In the assays conducted on organs obtained post mortem, the amounts of the drug in renal tissue were approximately double that in serum and smaller amounts were present in lung and heart muscle, while traces or none could be found in brain. It is perhaps of significance that the liver, an organ capable of altering many compounds, contained virtually no streptomycin.

The low plasma clearance values obtained for streptomycin explain its presence in the serum for as long as twelve hours following parenteral administration. It seems likely, however, that the high blood levels required in the treatment of infections [9] will necessitate frequent injections or continuous infusions in order that therapeutic levels may be maintained.

The data regarding diffusion of streptomycin into the spinal fluid are inconclusive and will require further elaboration before the therapeutic implications are clear. In the few studies reported here, it would seem that the presence of an inflammatory reaction in the meninges increases the diffusion of streptomycin into the spinal fluid.

SUMMARY

Data are presented regarding the absorption, distribution and excretion of streptomycin administered by various routes.

Streptomycin was not absorbed to any appreciable extent when given orally or by inhalation. Following parenteral administration, it was possible to demonstrate the material in the serum in amounts roughly proportional to the dose.

Streptomycin appeared in significant concentrations in the spinal fluid of 3 subjects with meningitis and in the pleural fluid of 2 subjects with pleural effusions. In 2 subjects streptomycin was demonstrated in the bile.

A study on the distribution of streptomycin in various organs obtained post mortem showed that it was present in the kidney in high concentration. Smaller amounts were found in the lung and in heart muscle, while both the brain and the liver contained virtually none.

From 41 to 86 per cent (mean 65 per cent) of the dose was excreted in the urine within twelve hours of the parenteral administration of streptomycin. Plasma clearance values ranged from 38 to 67 cc. of plasma cleared of streptomycin per minute.

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Progress in Internal Medicine

BLOOD

A Review of the Recent Literature

FRANK H. BETHELL, M.D.

CYRUS C. STURGIS, M.D.

R. WAYNE RUNDLES, Ph.D., M.D.
AND
MURIEL C. MEYERS, M.D.
ANN ARBOR, MICH.

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BONE MARROW

Osgood and Seaman[377] state after a review of the literature that wide discrepancies in the published values for normal marrow cells obtained by sternal puncture are due to uncritical acceptance of subjects as normal, differences in the quantity of material aspirated with a consequent variable degree of dilution of marrow with blood and lack of uniform criteria for identification of cells and terminology. They conclude that normal standards for aspirated marrow must await further studies. The authors advocate withdrawal of at least 1 cc. of material, since the cellular composition is not greatly affected by variations in volume in excess of 1 cc. The aspirated material should then be placed in a tube containing 2 mg. of potassium oxalate and thoroughly shaken. A count is made of nucleated cells, and films are prepared and stained with Wright's stain. Differential counts, which often are not necessary for diagnosis, should be made on at least 500 cells, utilizing the thin area of the film.

Two cases are reported by Schleicher[378] in which aspirated marrow revealed many giant orthochromatic erythroblasts. In 1 the diagnosis was reticulum cell sarcoma and in the other pernicious anemia. According to the author, such erythroblasts are not diagnostic of any disease but are an expression of a defunct reticulum. Interpretation of erythrogenesis should be based on the nuclear pattern of the early erythroid cells, including pronormoblasts and promegalo-

377. Osgood, E. E., and Seaman, A. J.: The Cellular Composition of Normal Bone Marrow as Obtained by Sternal Puncture, Physiol. Rev. **24**:46, 1944.

378. Schleicher, E. M.: Giant Orthochromatic Erythroblasts: Their Importance for the Promegaloblast and Pronormoblast Problem, J. Lab. & Clin. Med. **29**:127, 1944.

blasts. In another communication, Schleicher [379] states that the so-called azurophile granulation in the cytoplasm of proerythroblasts is essentially an artefact and indicates merely that the cells have reached a certain physicochemical phase in their development.

Mitotic division of marrow cells was studied by Forteza Bover.[380] He concludes that although mitosis can be observed in the hemocytoblasts of acute leukemia it is rare, and consequently the rapid proliferation of the cells must be accounted for by amitotic division. Atypical mitosis in the erythrocyte series occurs in a variety of severe blood disorders. It may be characterized by fragmentation, fusion, asymmetry and multipolar division. De Barros [381] discusses the development of the erythrocyte in normal circumstances and in pathologic conditions. He relates specific deficiencies to abnormalities of maturation and describes the resulting types of anemia. Vereby [382] advances the hypothesis that there exists in bone a substance which exerts a controlling influence on red marrow and is necessary for both the initiation and the maintenance of hemopoiesis.

Myeloid metaplasia associated with myelosclerosis is discussed by Oyanguren and Videla,[383] who review the literature dealing with this condition and report a case. Andersen and Lund [384] report a case of osteosclerotic anemia in a boy 17 months old. The clinical manifestations were anemia, fever and hemorrhages. Roentgen examination revealed pronounced periosteal deposits and large meshed structure of the substantia spongiosa. At necropsy extensive endosteal and periosteal osteosclerosis was found, together with fibrosis of the marrow. Many of the lymph nodes contained hemopoietic tissue, but there was no evidence of leukemia. Gormsen [385] reports 2 cases of myeloid metaplasia in the adrenal glands. In 1 case, that of a woman of 44 years, a single adrenal tumor consisting of hematopoietic tissue was found at necropsy. The patient died of a pulmonary embolus following hysterectomy for uterine fibroid. In the second case there was wide-

379. Schleicher, E. M.: Observations on the So-Called Azurophilic Granulation of Proerythroblasts, Anat. Rec. **87**:355, 1943.

380. Forteza Bover, J.: Estudio de las mitosis en las células de la serie roja y blanca de la médula ósea, Med. españ. **10**:790, 1943.

381. de Barros, N. V.: Fisiologia da eritropoiese, Folia clin. et biol. **14**:45, 1942.

382. Vereby, R.: Die Blutbildung im Knochenmark und die Knochensubstanz, Deutsche med. Wchnschr. **69**:660, 1943.

383. Oyanguren M., H., and Videla Z., P.: Anemia leuco-eritroblástica esplenomegálica del adulto por mieloesclerosis, Rev. méd. de Chile **71**:896, 1943.

384. Andersen, B., and Lund, T.: Osteosclerotic Anemia in a Boy of 17 Months, Acta path. et microbiol. Scandinav. **20**:425, 1943.

385. Gormsen, H.: Ueber das Vorkommen von hämopoietischem Gewebe in der menschlichen Nebenniere, Virchows Arch. f. path. Anat. **310**:369, 1943.

spread myeloid metaplasia with hemopoiesis occurring in both adrenal glands.

The characteristics of the marrow of a series of 100 elderly patients are reported by Reich, Swirsky and Smith.[386] They observed active hemopoiesis in these subjects, with no evidence of myeloid atrophy attributable to age. Cope [387] discusses the value of sternal aspiration as a diagnostic aid. Linhard [388] found that in cases of trypanosomiasis the organisms were much more numerous and more readily found in aspirated sternal marrow than in the peripheral blood. Meyer and Halpern [389] report the case of a 51 year old man with chronic myelogenous leukemia and myocardial disease, who died immediately after sternal puncture, apparently from cardiac failure.

Bloom and Meyer [390] present tables of normal cellular constituents of the marrow and peripheral blood of dogs. The specimens of marrow were obtained from the crest of the ilium. Yoffey and Parnell [391] obtained an average value of 469,000 nucleated cells per cubic millimeter of rabbit costal marrow, of which 61,000 were lymphocytes. Their data, it is concluded, lend support to the view that lymphocytes leave the blood to enter the bone marrow but they throw no light on the fate of the lymphocytes in the marrow.

LIPOID HISTIOCYTOSES

Niemann-Pick's Disease.—Canmann [392] reports a case of Niemann-Pick's disease and reviews much of the literature dealing with the subject. To date somewhat more than 60 cases of this disease have been reported. About half the patients have been members of the Jewish race, and in about one fourth of the cases there was a positive family history of the disorder. The disease has been uniformly fatal before the age of 30 months. The cherry red macular spot which occurs in both this disease and in Tay-Sachs disease is a helpful

386. Reich, C.; Swirsky, M., and Smith, D.: Sternal Bone Marrow in the Aged, J. Lab. & Clin. Med. **29**:508, 1944.

387. Cope, R. L.: Sternal Marrow Aspiration as an Aid in Diagnosis, Texas State J. Med. **40**:191, 1944.

388. Linhard, J.: Value of Sternal Puncture in Diagnosis of Trypanosomiasis, Trop. Dis. Bull. **41**:14, 1944.

389. Meyer, L. M., and Halpern, J.: Death Following Sternal Puncture, Am. J. Clin. Path. **14**:247, 1944.

390. Bloom, F., and Meyer, L. M.: The Morphology of the Bone Marrow Cells in Normal Dogs, Cornell Vet. **34**:13, 1944.

391. Yoffey, J. M., and Parnell, J.: The Lymphocyte Content of Rabbit Bone Marrow, J. Anat. **78**:109, 1944.

392. Canmann, M. F.: Niemann-Pick Disease (Acute Idiopathetic Xanthomatosis, Phosphatide Lipoidosis, Lipoid Cell Splenomegaly, Niemann Type), J. Pediat. **24**:335, 1944.

diagnostic sign. The pathogenesis of the disease is still open to investigation.

Canmann's patient was an infant who died at the age of 10 weeks, having been ill from the time of birth. The clinical diagnosis was congenital heart disease and hypothyroidism. At autopsy the heart and liver were found to be twice the normal size and the spleen three times normal size. Microscopic examination showed dissemination and infiltration of foam cells in all the organs and in the bone marrow.

Facatselli [393] summarized the clinical findings in Niemann-Pick's disease, discussed the interrelationships among the lipoid diseases, including Tay-Sachs disease, and reported a case of Niemann-Pick's disease in detail. His patient was a 14 month old girl, the first child of native Turks. There was no knowledge of familial diseases. The infant was well and strong until the age of 8 months, when progressive enlargement of the abdomen with failure of further body growth appeared. Examination showed the girl to be poorly nourished. The ocular fundi were normal and the inguinal lymph nodes moderately enlarged. There was an enormous enlargement of the spleen and liver. The examination of the peripheral blood showed the hemoglobin content to be 35 per cent and the red blood cells 2,700,000. The red blood cells showed great variation in staining and in size and shape, and a few were nucleated. Giant foam cells were obtained from the spleen, bone marrow and lymph nodes by puncture. Five-tenths cubic centimeter of splenic pulp was aspirated and subjected to a chemical analysis, which showed 2.74 per cent phosphatides and 0.046 per cent cerebrosides. The blood cholesterol level was 280 mg. per hundred cubic centimeters. The child finally died of an intercurrent infection at the age of 2½ years.

Von Cube, Schmitz and Wienbeck [394] report another case of Niemann-Pick's disease. The authors point out that this malady often cannot be diagnosed during life or distinguished from the infantile form of Gaucher's disease. The central red area in the macula is the only clinical sign differentiating the two diseases. They reported the case of a 2 year old child, the fourth and last sibling in a non-Jewish family. There were no known familial diseases. At the age of 9 months failure of the patient to gain weight led to the discovery of gross enlargement of the liver and spleen. The blood values, except for a leukopenia of 4,600, were normal. At the age of 1 year and 10 months the patient's development was further retarded and there was a serious feeding problem. At this time a moderately severe

393. Facatselli, N.: La maladie de Niemann-Pick (apropos d' un cas personnel), Ann. pædiat. **162**:218, 1944.

394. von Cube, R.; Schmitz, E., and Wienbeck, J.: Leichte bis mittelschwere Niemann-Picksche Krankheit, Virchows Arch. f. path. Anat. **310**:631, 1943.

hypochromic anemia was present, but sternal aspiration revealed normal marrow. The child died during an operation for removal of the spleen.

The spleen and brain were subjected to chemical analysis. A phosphatide, largely insoluble in ether, and cholesterol accounted for 91 per cent of the total lipids in the spleen. Microscopic study of the tissues revealed characteristic features of the disease, but they were less extensive than those in most reported cases. The brain showed no outstanding abnormalities.

Gaucher's Disease.—Fanconi [395] reported 2 cases of Gaucher's disease occurring in non-Jewish, healthy families. The first patient was a 5 year old girl who had enlarged lymph nodes and who became slightly jaundiced. Examination showed the liver and spleen to be enlarged, the lower borders lying some 5 cm. below their respective costal margins. The blood was normal, and tests of hepatic function showed no impairment of function. The blood cholesterol value was 362 mg. per hundred cubic centimeters. Both sternal puncture and splenic puncture revealed the presence of large Gaucher's cells. Roentgenograms of the skeleton were normal. His second case was a follow-up study of an 18½ year old girl whose spleen had been removed earlier in life because of Gaucher's disease. Her general condition had remained poor. Examination showed that she was poorly developed, infantile in build and slightly icteric. The edge of the liver lay 10 cm. below the right costal margin. There was a slight anemia present, and sternal aspiration revealed an infiltration of the bone marrow by Gaucher's cells. Roentgenograms of the chest showed that there was increased density in both pulmonary fields. There was thinning of the cortex and widening of the trabeculae in the ribs and in the carpal bones such as are seen in Cooley's anemia. The blood cholesterol level varied from 645 to 683 mg. per hundred cubic centimeters, more than double the preoperative level. The serum phosphatides were 36.8 mg. per hundred cubic centimeters, whereas the preoperative value was 18 mg. The author observed that the more frequently cases of lipoid disease are studied the less sharply defined are the various clinical types. In Gaucher's disease, since there is no alteration in the fundamental process accomplished by splenectomy, this operation should be delayed as long as possible.

Stehle [396] discussed at length the effect of splenectomy in Gaucher's disease, both the immediate effect and the long range influence on the natural course of the disease. He reported a late follow-up study of 2 cases in which splenectomy had been done early in life. His

395. Fanconi, G.: Zwei Fälle von Morbus Gaucher, Ann. pædiat. **162**:270, 1944.

396. Stehle, I.: Beiträge zur Morbus Gaucher: II. Die Folgen der Splenektomie beim Morbus Gaucher, Deutsche Ztschr. f. Verdauungskr. **7**:145-1943.

observations suggest that the skeletal changes which sometimes occur are a constitutional variant having no direct relation to forms of the disease characterized by splenomegaly and hepatomegaly. Splenectomy is beneficial in that it rids the patient of a bulky organ, and in many cases there has followed great improvement in the anemia, leukopenia and hemorrhagic tendency. The operation is regarded as a symptomatic measure in the treatment of this disease.

Levine and Solis-Cohen [397] observed a 29 year old woman in whom a slight injury produced a fracture of the humerus. A roentgenogram showed multiple areas of punctate osteolysis in the cortical and medullary portions of the shaft, with some destruction of the cortex and periosteum at the neck of the humerus. Similar lesions were widely spread throughout the opposite humerus as well as in the other long bones and in the skull. A biopsy from the fractured bones showed cells typical of Gaucher's disease.

Hand-Schüller-Christian Disease.—Many new cases of Hand-Schüller-Christian disease and the recently recognized variant of that disease, eosinophilic granuloma of bone, have been reported during the past year. Garrahan and his collaborators [398] had under their care a 2 year and 5 months old boy in whom an orbital tumor developed, with exophthalmos and polyuria. The urine and blood were normal. Multiple osseous lesions were demonstrated, and later a granulomatous cutaneous tumor developed. A biopsy was made and a diagnosis of Schüller-Christian's disease established, although the histologic observations were not entirely typical. Baeza Goñi and Espinoza Soto [399] report a fatal case of this disease in a 3 year old boy who had generalized enlargement of the lymph nodes and diabetes insipidus associated with cachexia. At autopsy lipoid cellular infiltrations were found in the lymph nodes, hypophysis, liver, spleen and bone marrow.

Michaud and Sorba [400] reported an unusual instance of cholesterosis with multiple localizations in a 34 year old woman. Her illness began with generalized cutaneous pruritus and jaundice. Fatigue and rarely a slight fever occurred. Examination showed diffuse xanthomatosis of the skin and mucous membranes and enlargement of the liver. Roentgenograms showed a bony defect at the vertex of the skull, but

397. Levine, S., and Solis-Cohen, L.: Gaucher's Disease, Am. J. Roentgenol. **50**:765, 1943.

398. Garrahan, J. P.; Lascano González, J. C.; Gambirassi, A., and Magalhaes, A.: Sobre el granuloma eosinófilo y la enfermedad de Hand-Schüller-Christian, Arch. argent. de pediat. **22**:3, 1944.

399. Baeza Goñi, A., and Espinoza Soto, J.: Reticuloendoteliosis lipoidica (enfermedad de Hand-Schüller-Christian atípica), Rev. chilena de pediat. **15**:437, 1944.

400. Michaud, L., and Sorba, M.: Cholestérinose à localisations multiples, Schweiz. med. Wchnschr. **73**:1184, 1943.

the bones were otherwise normal. The circulating blood values were normal except for 8 per cent reticulocytes. Sternal aspiration revealed an abundance of cells with xanthomatous inclusions. Several determinations of the blood cholesterol level ranged from 8.5 to 20 Gm. per thousand cubic centimeters. A biopsy of the skin showed a heavy infiltration of xanthomatous cells closely grouped about the blood vessels and under the epidermis. The authors regarded the case as an atypical form of the Hand-Schüller-Christian disease.

An authoritative and thorough review of the subject of eosinophilic granuloma of bone was published by Jaffe and Lichtenstein.[401] Their work has shown that in this disease one, several or many bones may be affected, but that the disease is limited to the bony tissue. They believe that this entity is the mildest expression of the peculiar inflammatory histiocytosis which occurs also in the more serious disease described under the names of Letterer-Siwe and Schüller-Christian. The changes in the blood are limited to an occasional instance of leukocytosis of moderate severity or to such changes as a slight increase in the eosinophilic granuloma developing under the mandible of a 24 year old man. There was an eosinophil count of 7 per cent in the case of this patient. The tumor was excised completely, and the patient remained well. Microscopic examination of the specimen showed that the granuloma had originated about a rudimentary tooth rest. Inclán and León[402] reported 2 cases of eosinophilic granuloma of bone in girls 3 years and 10 months old and 11 months old. The diagnosis was proved by biopsy in both cases. Examinations of the blood showed an eosinophilia of 3 to 4 per cent, and in 1 case the Rumpel-Leede phenomenon appeared.

Versiani, Figueiró and Junqueira[403] reported the occurrence of an eosinophilic granuloma of bone in a 50 year old Spanish woman. The first symptoms were stabbing pains in the left thigh. A roentgenographic examination showed a fusiform area of rarefied bone in the middle of the left femur, and for a time the patient's painful symptoms were relieved by antisyphilitic treatment. Nine months later, while hurrying to catch a train, she suffered a fracture through the diseased area of bone. A polyuria of over 5 liters per day was noted and success-

401. Jaffe, H. L., and Lichtenstein, L.: Eosinophilic Granuloma of Bone: A Condition Affecting One, Several or Many Bones, but Apparently Limited to the Skeleton, and Representing the Mildest Clinical Expression of the Peculiar Inflammatory Histiocytosis also Underlying Letterer-Siwe Disease and Schüller-Christian Disease, Arch. Path. **37**:99 (Feb.) 1944.

402. Inclán, A., and León, P. M.: Granuloma eosinófilo de los huesos, Cir. ortop. y traumatol., Habana **11**:58, 1943.

403. Versiani, O.; Figueiró, J. M., and Junqueira, M. A.: Hand-Schüller-Christian's Syndrome and "Eosinophilic or Solitary Granuloma of Bone," Am. J. M. Sc. **207**:161, 1944.

fully treated with posterior pituitary extract. Biopsy of the lesion in the femur showed granulomatous tissue infiltrated with eosinophils. There was no other bony lesion demonstrable by roentgenographic examination. In five months' time another examination showed slow, aberrant formation of bony callosity in the region of the fracture.

An eosinophilic granuloma producing neurologic signs and symptoms was reported by Osborne, Freis and Levin.[404] A 21 year old soldier had first a transient paralysis of the side of the face and four months later an acute attack of vertigo, at which time tenderness over the spine of the first thoracic vertebra was found. Tinnitus and pain in the ear developed subsequently. Roentgenograms of the skull showed destructive lesions in the left temporal bone, the mandible, the first, second and seventh cervical vertebrae, several ribs, the right femur and the transverse process of the fifth lumbar vertebra. There was no abnormality of the circulating blood except for an increased sedimentation rate. Two specimens for biopsy were taken from the mandible and one from the fifth rib. In each specimen there was destruction of bone and replacement with a gray granulation tissue, and microscopically the typical changes of eosinophilic granuloma were seen. Roentgen ray therapy was given, and four months later, eleven months after the initial symptoms, he was free of neurologic signs and symptoms and there was partial recalcification of the bony defects.

Thoma[405] treated an 8 year old child who had a fleshy tumor with destruction of the bone in the mandible and later with other destructive areas in the mandible, skull and pubic bone. Diabetes insipidus appeared. A biopsy of the mandible showed eosinophilic granuloma. Roentgen ray therapy was followed by definite improvement.

HEMORRHAGIC DISORDERS AND COAGULATION OF BLOOD

General Observations.—The factors and mechanisms involved in the coagulation of blood continue to engage the interest of many investigators. Recent studies have been concerned not only with the factors having to do with the production of a clot but also with those which prevent coagulation in vivo. However, precisely what acts as the trigger in initiating coagulation and whence this substance is derived are still not known. Quick[406] reviews the literature that

404. Osborne, R. L.; Freis, E. D., and Levin, A. G.: Eosinophilic Granuloma of Bone Presenting Neurologic Signs and Symptoms: Report of a Case, Arch. Neurol. & Psychiat. **51**:452 (May) 1944.

405. Thoma, K. H.: Eosinophilic Granuloma with Report of One Case Involving First the Mandible, Later Other Bones, and Being Accompanied by Diabetes Insipidus, Am. J. Orthodontics (Oral Surg. Sect.) **29**:641, 1943.

406. Quick, A. J.: Blood, in Luck, J. M.: Annual Review of Physiology, Stanford University, Calif., Annual Reviews, Inc., 1944, vol. 6, p. 295.

has appeared since his excellent monograph in 1941. He emphasizes the controversy attendant on the commonly accepted theories as to the mechanism of coagulation and reviews the current status of knowledge regarding prothrombin, platelet activity and the various anticoagulants. He reports further experimental evidence [407] that prothrombin is composed of two factors, A and B, which are combined through calcium. The factor which disappears in decalcified stored blood is designated component A. Component B is the factor which disappears after feedings of dicoumarin and in vitamin K deficiency. Therefore stored blood and plasma should be effective in treating the hypoprothrombinemia produced by dicoumarin.

Quick was able to confirm the work of Bay, Tanturi and Banfi,[408] who found that peptone shock, induced in dogs by Witte's peptone, was accompanied with an increase in the coagulation time. This increase and its persistence varied directly with the dose of peptone used. Reinjection of peptone into an animal after twenty-four hours showed that the first injection had produced a relative state of immunity as far as modification of coagulation time was concerned. An anticoagulant, probably heparin, was thought to be liberated on the injection of the peptone. No alteration in prothrombin concentration was demonstrated.

Antithrombin content of the blood and its relation to heparin are also discussed by Volkert,[409] who noted that on intravenous injection of solutions of albumin antithrombin increases of 60 to 70 per cent, lasting two or three hours, occurred experimentally. Subsequent injections resulted in transient increases of only 10 per cent in antithrombin. Volkert considers that this change in antithrombin is related to hypersensitivity. The injection of pneumococcic antigen or other protein as well as anaphylactic reactions caused transient increases in the antithrombin content of the blood. The role of histamine as an anticoagulant has been considered by de Takáts,[410] who investigated the effect of stimulating the cholinergic and adrenergic components of the autonomic nervous system on the clotting mechanism. Adrenergic stimuli were observed to increase and cholinergic stimuli to decrease the tendency to postoperative thrombosis. These phenomena were thought to be correlated with the fact that histamine closes and epinephrine

407. Quick, A. J.: Constitution of Prothrombin and Its Clinical Significance, J. A. M. A. **124**:734 (March 11) 1944.

408. Bay, R.; Tanturi, C. A., and Banfi, R. F.: El tiempo de coagulación y la protrombina en el shock peptónico, Medicina, Buenos Aires **4**:267, 1944.

409. Volkert, M.: Der Antithrombingehalt des Blutes und seine Beziehung zum Heparin, Biochem. Ztschr. **314**:34, 1943.

410. de Takáts, G.: Nervous Regulation of Clotting Mechanism, Arch. Surg. **48**:105 (Feb.) 1944.

opens the sphincters controlling venous outflow from the liver. Since plasma prothrombin is manufactured to a great extent in the liver, it is possible that by neurogenic control the rate of its discharge from the liver may be influenced, with falls in plasma prothrombin with histamine stimulation, shock and anaphylaxis and rises in plasma prothrombin with epinephrine stimulation, excitement and fear.

Antithrombin is believed to consist of two components, one variable and the other constant. The exact nature of either is unknown, but de Sütö-Nagy [411] presents evidence in support of the theory that sphingomyelin, derived from tissue albumin, may be a natural antithromboplastin, or thrombin inhibitor. Removal of sphingomyelin, or inactivation of thromboplastin and calcium, may be the necessary first step for the activation of thrombin in setting off the coagulation mechanism. Feissly [412] believes that the classic theory of coagulation of the blood, in which prothrombin activation is attributed entirely to the disintegration products of platelets under set circumstances, must be seriously doubted. He has been able to confirm the presence in normal plasma of a prothrombin activator which differs from the prothrombin activator obtained from platelet extract. The former is thermolabile and probably protein in nature; the latter is thermostabile and probably a lipid. He suggests, therefore, that, whereas platelets and their disintegration products are capable of accelerating the clotting process, other factors are concerned in its initiation. Further studies along this line of reasoning have been conducted by Adams following the observation of Parfentjev in 1941 that a pseudoglobulin fraction obtained from plasma from rabbits had a pronounced coagulative activity on normal human oxalated blood. This pseudoglobulin fraction showed excellent hemostatic activity in small wounds. When the substance was given by mouth in large doses, a decrease in the coagulation time of the circulating blood was noted. The more recent study by Adams and Taylor [413] shows that plasma from both beef and swine may be used as a source of a pseudoglobulin possessing thrombic activity similar to that of plasma from rabbits but that preparations from these animals require more purification than do those from rabbits.

Under physiologic conditions, calcium is indispensable for coagulation of the blood. Although oxalated plasma will not clot spontaneously, it has been known that contamination with certain organisms,

411. de Sütö-Nagy, G. J.: Mode of Action of Anti-Coagulant Derived from Tissues, Am. J. Physiol. **141**:338, 1944.

412. Feissly, R.: Sur la thrombokinase plasmatique, Helvet. med. acta **10**:3, 1943.

413. Adams, M. A., and Taylor, F. H. L.: The Thrombic Activity of a Globulin Fraction of the Plasma Proteins of Beef, Swine and Human Blood, Am. J. M. Sc. **205**:538, 1943.

such as staphylococci, will produce coagulation. Fredericq [414] reports studies concerning this type of coagulation in the absence of calcium and concludes that the coagulase produced by the bacteria replaces thrombin in the clotting mechanism and directly activates fibrinogen. The relation, if any, of coagulase to thrombin is unknown.

Since 1938 there have appeared in the literature reports dealing with the presence in acetone extracts of spleens from patients with idiopathic thrombopenic purpura of a substance which would cause a definite transient lowering of platelets when injected into rabbits. Cronkite [415] believed he was able to confirm the presence of "thrombocytin" in extracts of spleens removed from patients with idiopathic thrombocytopenic purpura and from 1 patient with chronic malignant neutropenia, but from extracts of spleens of patients with tuberculosis of the spleen, clinically indistiguishable from idiopathic thrombocytopenic purpura, no such effect was obtained.

Werner [416] has studied the blood platelets and clot retraction and reports that the retraction ferment of platelets cannot be extracted.

Øllgaard [417] observed that if citrated blood is allowed to settle at 42 C. for three hours and if small amounts of mercuric cyanide or saponin are then added platelet agglutination develops to so pronounced a degree as to be macroscopically visible. The degree of agglutination among normal persons was observed to be extremely variable. In women up to the thirtieth year it is strongest. The addition of heparin to the plasma completely inhibits the platelet-agglutinating activity of mercuric cyanide and saponin.

A definite clinical contribution is the work of G. and R. Reimann-Hunziger,[418] who studied the effect of surgical procedures on the platelet counts of 30 patients. Counts were done immediately before operation and one hour and three days after operation. The type of illness, operation or anesthesia did not appear to influence the counts. Although most patients showed a slight increase in the number of platelets immediately postoperatively, their values dropped to normal by the third day. The author believes that those patients showing thrombocytosis as late as the third day should be considered as candidates for prophylactic heparinization because of the potential danger of pulmonary embolism.

414. Fredericq, P.: La coagulation du sang en l'absence de calcium, Arch. internat. de physiol. **52**:73-152, 1942.

415. Cronkite, E. P.: Further Studies of Platelet Reducing Substances in Splenic Extracts, Ann. Int. Med. **20**:52, 1944.

416. Werner, H.: Strukturgebundene Fermentwirkung der Thrombozyten, Deutsche med. Wchnschr. **70**:155, 1944.

417. Øllgaard, E.: Untersuchungen über die Agglutination der Blutplättchen, Klin. Wchnschr. **22**:80, 1943.

418. Reimann-Hunziger, G., and Reimann-Hunziger, R.: Ueber das Verhalten der Blutplättchen vor und nach Operationen, Wien. klin. Wchnschr. **57**:62, 1944.

An unusually interesting study is that of de Takáts, Trump and Gilbert,[419] who, because of the frequent observation of the sudden development of embolic phenomena in patients who have had auricular fibrillation for many years and because of the fact that some of these patients had been receiving digitalis, studied the effect of digitalis on the clotting mechanism. With use of the heparin tolerance test, digitalis was shown to have a counteracting effect on the anticoagulant activity of heparin in both animals and human beings. The mechanism by which digitalis opposes heparin in the coagulation system is not known. Specific thromboplastic properties or efficiency in mobilization of prothrombin from the liver are suggested.

Massie and others [420] also report that the administration of digitalis causes a decrease in the clotting time of the blood. In studying 35 patients of both sexes, with and without heart disease, ranging in age from 24 to 78 years, Massie and his associates could demonstrate no alteration in prothrombin time or in clot retraction before and after digitalization. The general condition of the patient, degree of reaction to the drug and presence or absence of failure had no detectable effect on the coagulation-accelerating effect of digitalis. It is suggested that the digitaloid drugs may have a thromboplastic effect because of some specific action antagonistic to heparin.

A technic for the determination of increased coagulability of the blood to be used as an adjunct in the study of thrombosis in digitalized patients is described by Waugh and Ruddick.[421]

Shapiro [422] describes a single stage method of prothrombin estimation of great sensitivity, which he advocates for serial estimations for postoperative and postpartum patients for the early detection of a thrombogenic state (reactive hyperprothrombinemia) in order that anticoagulant therapy may be instituted early and extension of thrombotic processes be avoided.

Purpura.—There have been but few publications and no important new contributions dealing with essential thrombopenic purpura in the past year. Limarzi [423] and Farrar and Roxby [424] have published gen-

419. de Takáts, G.; Trump, R. A., and Gilbert, N. C.: The Effect of Digitalis on the Clotting Mechanism, J. A. M. A. **125**:840 (July 2) 1944.

420. Massie, E.; Stillerman, H. S.; Wright, C. S., and Minnich, V.: Effect of Administration of Digitalis on Coagulability of Human Blood, Arch. Int. Med. **74**:172 (Sept.) 1944.

421. Waugh, T. R., and Ruddick, D. W.: Test for Increased Coagulability of Blood, Canad. M. A. J. **50**:547, 1944.

422. Shapiro, S.: Hyperprothrombinemia, Premonitary Sign of Thrombo-Embolization (Description of Method), Exper. Med. & Surg. **2**:103, 1944,

(Footnotes continued on next page)

eral papers on purpura, reviewing the current status of diagnosis and management of the thrombopenic purpuras particularly. Farrar and Roxby stress the necessity for complete etiologic diagnosis, reiterating that splenectomy is indicated only in treatment of patients with idiopathic thrombopenic purpura. In treatment of secondary purpuras therapy consists of amelioration or correction of the primary difficulty. Kracke [425] believes transfusion of fresh whole blood is the medical method of choice in staying bleeding. With the use of prophylactic transfusions White [426] reports the uneventful extraction of a tooth from a patient with long-standing severe thrombopenic purpura. Whether or not the thrombopenia was primary is not stated. Emphasis is placed on the major surgical hazards which even minor procedures in these patients present.

Purpura as a complication of pregnancy and the probable status of the children born of such mothers continue to be subjects of concern to the internist, surgeon, obstetrician and pediatrician alike. The paucity of available reports precludes any gross generalizations, but from the report of Burnett and Klass [427] it is apparent that it is possible for a pregnancy complicated by purpura to terminate in the birth of a healthy child with normal blood values. Finn [428] believes the likelihood of having a normal baby is best if the disease is in a chronic phase or if splenectomy is done prior to pregnancy. His opinion is based on the study of 13 cases of thrombopenic purpura complicated by pregnancy, in which there were 5 infant deaths. However, only 1 of these could be attributed to congenital thrombopenic purpura. Of the 8 surviving infants, 1 had frank bleeding and 1 had petechiae. Polowe [429] reports a case of pregnancy complicated by thrombopenic purpura successfully treated by splenectomy in the eighth month of gestation. The patient gave birth twelve days later to a small but normal infant.

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423. Limarzi, L. R.: Hemorrhagic Diseases, Dent. Outlook **31**:142, 1944; Thrombocytopenic Purpura, M. Clin. North America **28**:153, 1944.

424. Farrar, G. E., Jr., and Roxby, J. B., Jr.: The Management of Purpura, Clinics **2**:1295, 1944.

425. Kracke, R. R.: Diagnosis and Treatment of the Bleeding Diseases, J. South Carolina M. A. **40**:1, 1944.

426. White, J. W.: Thrombocytopenic Purpura and Tooth Extraction, Brit. M. J. **2**:341, 1944.

427. Burnett, C. W. F., and Klass, I.: A Review of the Problem of Purpura During Pregnancy, J. Obst. & Gynaec. Brit. Emp. **50**:393, 1943.

428. Finn, W. F.: Thrombocytopenic Purpura in Pregnancy: Review of the Literature with a Report of Three Cases, Am. J. Obst. & Gynec. **48**:497, 1944.

429. Polowe, D.: Splenectomy in Pregnancy Complicated by Thrombocytopenic Purpura Hemorrhagica: Report of a Successful Case, with a Review of the Literature, J. A. M. A. **124**:771 (March 18) 1944.

Unusual instances of symptomatic thrombopenic purpura include those reported by Pérez Castañeda,[430] who had 4 patients with vitamin C deficiency associated with thrombopenia and bleeding. The intravenous administration of ascorbic acid was followed by increased platelet counts and the cessation of bleeding.

Conklin and Shank [431] report a case of thrombopenic purpura complicating exophthalmic goiter in a 36 year old woman. Unfortunately the patient's condition precluded studies of the bone marrow. However, no pathologic cells were found in the blood. After surgical removal of the thyroid, although thrombopenia persisted, the patient became asymptomatic.

Woodward [432] reports the occurrence in a 14 year old boy of acute catarrhal jaundice complicated by thrombopenic purpura and followed by an uneventful recovery with conservative management. He considers that the thrombopenia was due not to impaired hepatic function alone but to a general disturbance of the reticuloendothelial tissue associated with generalized lymphadenopathy and splenomegaly. In a search of the literature he found the report of only 1 similar case.

Rhodes and Borelli [433] report an instance in an infant of giant hemangioendothelioma (confirmed by biopsy) associated with thrombopenic purpura. High voltage roentgen therapy caused regression of the tumor mass and restoration of the blood picture to normal.

Purpura as a complication of malaria is reviewed by Greco and Ziedman.[434] They report a case of purpura symptomatica (Henoch-Schönlein type) complicating therapeutic quartan malarial fever. The drugs the patient received before purpura developed, bismuth subsalicylate, sodium chloride and dextrose and a mixture of acetylsalicylic acid, acetophenetidin and caffeine, were exonerated, because they were readministered after his recovery without ill effect. Quinacrine hydrochloride, first given after the onset of purpura, failed to stop the progress of the lesions or to control the malaria. Quinine promptly halted the malarial

430. Pérez Castañeda, L.: Avitaminosis púrpuro-hemorrágica, Med. españ. **4**:193, 1940.

431. Conklin, S. D., and Shank, P. J.: Thrombocytopenic Purpura Associated with Exophthalmic Goiter: A Review of the Available Literature and a Case Report, Ohio M. J. **40**:47, 1944.

432. Woodward, T. E.: Thrombocytopenic Purpura Complicating Acute Catarrhal Jaundice: Report of a Case, Review of the Literature and Review of Forty-Eight Cases of Purpura at University Hospital, Baltimore, Ann. Int. Med. **19**:799, 1943.

433. Rhodes, A. W., and Borelli, F. J.: Giant Hemangio-Endothelioma with Thrombocytopenic Purpura: Results of Roentgen Therapy, Am. J. Roentgenol. **52**:323, 1944.

434. Greco, A. J., and Ziedman, I.: Purpura as a Complication of Malaria, M. Bull. Vet. Admin. **20**:457, 1944.

fever and the purpura. Although severe purpura is considered an indication for interruption of therapeutic malaria, it is suggested by these authors that further study be undertaken to determine whether such patients can tolerate malaria at later dates.

The effect of splenic irradiation on increased vascular erythropermeability in purpura was studied by Madison, Squire and Morton [435] in 16 cases of purpura, entirely unselected for presence or absence of coexisting defects of coagulation. Splenic irradiation was given in doses of 50 to 200 r, with voltage of 140 peak kilovolts and filter of 0.25 mm. of copper every second or third day for three to five doses. All patients were kept under observation for "a considerable period," and changes in the blood vessels and the blood were frequently checked. Thirteen patients showed moderate to pronounced reversal of the vascular lesion, whereas 3 showed minimal or no response. In analysis, the authors concluded that in those patients whose conditions responded to roentgen therapy the lesions were essentially benign and reversible, many allergic in origin, and that in those whose conditions failed to respond the lesions represented purpura secondary to leukemia. It is suggested that irradiation may be a valuable measure in stopping spontaneous vascular leakage in selected cases of purpura, whether or not failure to respond to splenic irradiation strongly points to purpura secondary to progressive or malignant disease.

A special group of purpuras associated with infection is recognized under the name, Waterhouse-Friderichsen syndrome. According to Bush and Bailey,[436] Voelcker in 1894 was the first to describe the symptom complex of a fulminating febrile illness with purpuric eruption and bilateral adrenal hemorrhages. Waterhouse reported a case in 1911 and Friderichsen in 1918. The syndrome, subsequently called Waterhouse-Friderichsen, was for many years considered universally fatal, and Motsay and Crispell [437] state that of the 125 cases reported up to October 1943 90 per cent had been of children under 9 years of age. Of interest, therefore, are the recent reports of the syndrome in adult patients and of recovery. Although there are no pathognomonic or even uniform hematologic changes, the syndrome is considered here because of the prominence of the purpuric manifestations.

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435. Madison, F. W.; Squire, T. L., and Morton, S. A.: Effect of Splenic Irradiation on Increased Vascular Erythropermeability in Purpura, J. A. M. A. **124**:735 (March 11) 1944. Madison, F. W.: Present Status of Hemorrhagic Diseases, Wisconsin M. J. **43**:688, 1944.

436. Bush, F. W., and Bailey, F. R.: Treatment of Meningococcus Infections with Especial Reference to Waterhouse-Friderichsen Syndrome, Ann. Int. Med. **20**:619, 1944.

437. Motsay, D. S., and Crispell, K. R.: The Waterhouse-Friderichsen Syndrome: Acute Bilateral Adrenal Hemorrhage, Guthrie Clin. Bull. **13**:140, 1944.

A general summary of the clinical picture of the syndrome is presented by Kasich and Disick,[438] together with detailed clinical and pathologic observations in 2 cases of young men aged 18 and 21 years. These authors believe the cause of hemorrhage into the adrenal glands is overwhelming toxemia, since it has been demonstrated that purpuric reactions can be produced in animals by injection of bacterial autolysates. Since the adrenal glands are among the most vascular organs in the body, it is postulated that the same factors producing purpura may also cause the adrenal hemorrhage. They consider the basis of the bleeding tendency from two aspects: (1) changes in the number of platelets in the circulating blood and toxic depression of the bone marrow and (2) injury to the capillary endothelium.

Thomas and Leiphart [439] report 2 cases of Waterhouse-Friderichsen syndrome in adults and consider in detail the role played by the adrenal glands. They reject destruction of the adrenal glands by hemorrhage as the cause of rapid death in the syndrome, which they believe is due to overwhelming sepsis and toxemia. They point out that of patients whose deaths are characterized by the same clinical features the clinician is unable to predict which will and which will not be found to have adrenal hemorrhages at autopsy and that, whereas adrenalectomized dogs may live for days, patients with Waterhouse-Friderichsen syndrome usually die within a matter of hours.

Bush and Bailey [436] present in detail 6 typical cases of Waterhouse-Friderichsen syndrome in 2 of which the patients recovered and in 4 of which they died. In the 4 fatal cases, 3 of the patients had bilateral and 1 had unilateral adrenal hemorrhage. Therapy in all instances consisted of intramuscular administration of desoxycorticosterone and adrenal extract, intravenous injections of sulfadiazine, meningococcus antitoxin, fluids and whole blood and oxygen inhalations, necessary to combat cyanosis and anoxemia.

Another patient with the syndrome who was successfully treated by a similar regimen is reported by Potter and Bronstein.[440] They believe that plasma is of especial value in combating shock, since the danger of

438. Kasich, M., and Disick, S.: Meningococcemia with Bilateral Adrenal Hemorrhage (Waterhouse-Friderichsen Syndrome): Report of Two Cases. J. Tennessee M. A. **36**:464, 1943.

439. Thomas, H. B., and Leiphart, C. D.: Septicemia and Purpura with Adrenal Hemorrhage in the Adult (Waterhouse-Friderichsen Syndrome): A Discussion of the Role Played by the Adrenal Gland in the Production of the Syndrome; Report of Two Adult Cases, J. A. M. A. **125**:884 (July 29) 1944.

440. Potter, H. W., and Bronstein, L. H.: The Waterhouse-Friderichsen Syndrome: Report of a Case Terminating in Recovery, J. Lab. & Clin. Med. **29**:703, 1944.

water intoxication from overdosage with desoxycorticosterone is thereby obviated.

A fatal instance of Waterhouse-Friderichsen syndrome, unusual because it occurred in a woman 52 years old, is reported by Simmel.[441] The diagnosis was confirmed at autopsy.

Bernhard and Jordan [442] report 4 cases of Waterhouse-Friderichsen syndrome occurring in adults, with observations from autopsy. In 2 of these the meningococcus was isolated as the etiologic agent; in the other 2 the cause was not determined.

Humphrey and Toomey [443] report an instance of early recognition of meningococci in Waterhouse-Friderichsen syndrome by means of smears of the purpuric lesions stained with Wright's stain. This is significant because the symptoms of the syndrome are so protean and the course so fulminating that probably the greatest impediment to successful therapy is that the time taken to establish the diagnosis is frequently greater than that required for the syndrome to run its fatal course. Therefore, it is suggested by Motsay and Crispell [437] that adrenal replacement therapy should not be withheld until the diagnosis is established but that it be given on suspicion of the presence of Waterhouse-Friderichsen syndrome. Although the meningococcus is the most common etiologic agent, other organisms are not infrequently found; and in some instances, as in the 4 year old patient with fulminating fatal pyrexia with purpura and adrenal hemorrhages, reported by Schroder and Wells,[444] no definite etiologic agent may be demonstrated. However, successful treatment despite failure to demonstrate the causative agent is reported by Rucks and Hobson.[445]

The case of a 30 year old soldier with congenital syphilis, in whom thrombopenic purpura developed after treatment with arsenic and bismuth for eighteen months, is reported by Lewis.[446] The patient had all the classic features of the disease, with a platelet count of 3,000 per

441. Simmel, H. E.: Meningococcic Adrenal Purpura in Adults, Ohio State M. J. **40**:23, 1944.

442. Bernhard, W. G., and Jordan, A. C.: Bilateral Adrenal Hemorrhage (Waterhouse-Friderichsen Syndrome) Associated with Meningococcal Septicemia: Report of Four Cases in Adults with Review of Literature, J. Lab. & Clin. Med. **29**:357, 1944.

443. Humphrey, A. A., and Toomey, L. O.: Meningococcemia with Waterhouse-Friderichsen Syndrome: Early Recognition by Means of Buffy Layer Smears, U. S. Nav. M. Bull. **42**:165, 1944.

444. Schroder, C. H., and Wells, A. H.: Bilateral Adrenal Hemorrhages with Waterhouse-Friderichsen Syndrome, Minnesota Med. **27**:486, 1944.

445. Rucks, W. L., and Hobson, J. J.: Purpura Fulminans (Waterhouse-Friderichsen Syndrome): Case Report, Memphis M. J. **19**:18, 1944.

446. Lewis, G. M.: Thrombocytopenic Purpura Following N. A. B. Injections, Brit. M. J. **1**:13, 1944.

cubic millimeter and profuse bleeding into the skin and from the gums and hematuria. The illness terminated fatally despite several blood transfusions. Necropsy showed the usual changes of such a purpura. Reference is made to a publication of Bamforth and Elkington,[447] in which 4 cases were reported and 19 cases were collected from the literature, of which 10 were fatal. They also refer to the publications of Scarborough and Stewart [448] and Scarborough and Horne,[449] in which it is claimed that vitamin P (hesperidin) is of value in the treatment of purpura occurring as a manifestation of poisoning with arsenic and bismuth in the treatment of syphilis.

Hemophilia.—Hemophilia has received little consideration in the recent literature. No new criteria for diagnosis have been established, nor have any new therapeutic measures been introduced. Kocar [450] has studied marrow material obtained by sternal puncture from persons with hemophilia, and reports that the megakaryocytes are increased and have either multilobed nuclei or multiple nuclei and that involution forms are rare. The red blood cells are frequently polychromatophilic, and an increase in lymphocytes is seen, but no diagnostic abnormalities could be noted.

The blood platelets in patients with hemophilia have been studied extensively in the past, but in most of the reports it has generally been considered that they carry out their mission in the coagulation process as individual agents rather than as agents linked in conjunction with the other formed elements of the blood. Assuming from the knowledge now available that in order for blood to clot a sudden and massive disintegration of platelets is necessary, Pennell [451] describes a conjunction phenomenon between platelets and red cells, which he regards as a mechanism by which the platelets can employ the surfaces of the red cell for the contact necessary to carry out mass disintegration of platelets. Since platelets of hemophiliac patients have been shown to be normal in various ways, it is suggested that red cells of hemophiliac persons may be responsible for diminished red cell—platelet conjugation in the disease. Pennell found the phenomenon to be decidedly reduced in

447. Bamforth, J., and Elkington, J. St. G.: Arsenobenzol Purpura, with Short Description of Four Cases, Quart. J. Med. **24**:381, 1931.

448. Scarborough, H., and Stewart, C. P.: Effect of Hesperidin (Vitamin P) on Capillary Fragility, Lancet **2**:610, 1938.

449. Scarborough, H., and Horne, G.: Capillary Resistance in Toxic Manifestation of Antisyphilitic Therapy, Lancet **2**:66, 1940.

450. Kocar, J.: Ueber die Sternalpunktion bei Hämophilie, Folia haemat. **67**: 325, 1943.

451. Pennell, S.: A Platelet-Red Cell Conjugation Phenomenon and Its Relation to Blood Coagulation, Am. J. M. Sc. **205**:562, 1943.

patients with hemophilia and relatively increased in patients with thrombopenic purpura.

Feissly [452] suggests that in hemophiliac patients the serum albumin may play some role in the defective clotting mechanism.

Reports of cases of hemophilia by Echterracht [453] include an unusual instance of pseudotumor of bone (tibia) in a 13 year old child with hemophilia, with a description of clinical and roentgenologic features and of observations at autopsy. The tibial mass was thought by the orthopedist to represent hemangioma of the bone, osteomyelitis or osteogenic sarcoma, and by the roentgenologist, sarcoma of the tibia. The pathologic finding was a multilocular cavity occupied by a mass of deep red, jelly-like clotted blood forming the "tumor."

The management of hemophiliac patients continues to present a major problem. Many agents have been recommended for their treatment. With the exception of transfusions of blood and plasma, none have stood the test of time. The advent of the blood bank has made this type of treatment easily available, and it would now seem feasible to employ transfusions prophylactically rather than to restrict their use to emergencies. Munro and Jones,[454] in 1943, reported on a patient who apparently became refractory to repeated prophylactic transfusions. Poncher,[455] on the other hand, advocates their use in an attempt to keep the coagulation time as close to normal as possible and reports no untoward results with this type of management. Ratkovits [456] reports gratifying results in the treatment of a single patient with the oral and intramuscular administration of fresh raw mother's milk, which is said to contain a thermolabile zymoplastic substance. Such therapy has apparently been used for many years as part of the folklore of continental Europe.

It is known that suitable quantities of trypsin will reduce to normal, in vitro, the prolonged clotting time of hemophiliac blood. Tagnon [457] demonstrated a significant although transitory shortening of the coagulation time following intravenous injection of trypsin in 2 of 3 hemophiliac

452. Feissly, R.: Nouvelles etudes sur l'hemophilie; role des albumines plasmatiques dans la formation de la thrombine, Helvet. med. acta **11**:177, 1944.

453. Echterracht, A. P.: Pseudotumor of Bone in Hemophilia, Radiology **41**:565, 1943.

454. Munro, F. L., and Jones, H. W.: Detrimental Effect of Frequent Transfusions in Treatment of Patients with Hemophilia, Am. J. M. Sc. **206**:710, 1943.

455. Poncher, H. G.: Diseases of Blood in Infants and Young Children, Including the Hemorrhagic States, J. Pediat. **23**:680, 1943.

456. Ratkovits, H.: Zur Behandlung der Hämophilia, Wien. med. Wchnschr. **56**:728 1943.

457. Tagnon, H. J.: Effect of Intravenous Injection of Trypsin on the Blood Coagulation Time in Hemophilia, Proc. Soc. Exper. Biol. & Med. **57**:45, 1944.

persons. The effectiveness of such treatment did not compare with that of transfusion of blood or plasma, and the toxicity of trypsin by the intravenous route is so great that extreme caution must be observed in its use.

Hereditary Hemorrhagic Telangiectasia.—A review of the literature dealing with hereditary hemorrhagic telangiectasia from 1933 to 1944 is presented by Stock,[458] and 7 new cases are added. The possible relation between Osler's disease and other diseases, due not only to possible mesenchymal dysplasia but also to associated ectodermal dysplasia, is pointed out. Stock notes that in about 20 per cent of the recorded cases there is probably a total absence of a family history. Whether the patients in these cases can transmit the disease to their progeny is not known. The third recorded instance in the past eleven years in which the disease can be traced through six generations in one family is presented. The extreme rarity of this occurrence and the fact that the disease has become progressively milder during the last two generations in this family suggest self limitation of the hereditary transmission of the disease.

Another comprehensive review of literature dealing with hereditary hemorrhagic telangiectasia, including the history of the entity, synonyms, symptoms, sites of bleeding, diagnosis, prognosis, pathology and treatment, is presented by Barrock.[459]

Campbell [460] reports a case of hereditary familial telangiectasia with epistaxis and migraine which had been present in a 23 year old man since the age of 14. There was bleeding from the nose once each week, which was invariably preceded by typical migraine lasting half an hour to five hours, with relief after spontaneous epistaxis. The case is of special interest in that the nasal bleeding occurred in relation to the vasodilatation accompanying migraine. The family history showed that other members were affected by telangiectasia, but no statement is made as to other instances of migraine in the family.

Another interesting patient with hereditary familial telangiectasia is reported on by Wolfsohn.[461] There was a scarcity of telangiectasia in the skin, but an abundance of them in the mucous membrane of the upper part of the gastrointestinal tract, observed by gastroscopic examination. There were repeated hematemeses over a period of twelve

458. Stock, M. F.: Hereditary Hemorrhagic Telangiectasia (Osler's Disease): A Review of the Literature and Report of Cases, Arch. Otolaryng. **40**:108 (Aug.) 1944.

459. Barrock, J. J.: Hereditary Hemorrhagic Telangiectasia: Report of Case with Review of Literature, Wisconsin M. J. **43**:805, 1944.

460. Campbell, A. M. G.: Hereditary Familial Telangiectasis with Epistaxis and Migraine, Lancet **2**:502, 1944.

461. Wolfsohn, H.: Hereditary Familial Telangiectasis, Lancet **2**:581, 1944.

years, culminating fatally when the patient was 57. Such hereditary hemorrhagic telangiectasis in older persons is considered by Cutler [462] to exist in three forms: (1) an asymptomatic form, (2) a form characterized by mild bleeding amenable to local measures, such as radium cautery and cotton packs, helped by precautionary use of liquid petrolatum for crusts and (3) a form characterized by severe exsanguinating epistaxis, seen usually in persons in the age group of 45 to 60 in whom vascular changes play a prominent part and in whom the mortality is 4 per cent. The author considers repeated transfusions as mandatory and radium of variable and questionable value in treatment of the last form.

The Role of Vitamins in Coagulation of the Blood.—The part played by vitamins other than vitamin K in regard to bleeding has received but little attention during the past year. In an investigation of the mechanism responsible for the spontaneous hemorrhage caused by hypervitaminosis A, Light, Alscher and Frey [463] found overdosage of vitamin A to cause hypoprothrombinemia. In rats the effect of this overdosage can be controlled by simultaneous administration of a preparation of vitamin K (2-methyl-3-phytyl-1,4-naphthoquinone). However, there is no evidence that vitamin K is effective in preventing any of the other symptoms of toxicity occasioned by hypervitaminosis A, nor is it understood whereby vitamin K counteracts vitamin A in its production of hypoprothrombinemia.

In view of clinical reports on alteration of vascular permeability, or fragility, by various citrus products, a method was developed by Majovski and others [464] which can be used to show the protective action of certain peel fractions (vitamin P) in controlling vascular fragility. When air is suddenly evacuated from a jar in which mice are placed, hemorrhage occurs into the lungs of these mice. Crude hesperidin obtained from oranges and a water-soluble extract of lemon peel afforded protection to mice against this hemorrhage for a period of two to four hours after their administration. Pure hesperidin had little or no protective effect, but during the first two hours after its administration a greater degree of hemorrhage was apparent.

Having previously noted that total or partial depletion of vitamin C in guinea pigs produced no change in the prothrombin level and that

462. Cutler, M. H.: Hereditary Hemorrhagic Telangiectasia, Arch. Otolaryng. **40**:428 (Nov.) 1944.

463. Light, R. F.; Alscher, R. P., and Frey, C. N.: Vitamin A Toxicity and Hypoprothrombinemia, Science **100**:225, 1944.

464. Majovski, G. J., and others: Vascular Fragility and Permeability as Influenced by Various Agents: Description of Experimental Method and of Effects of Various Substances Related to Vitamin P, J. Pharmacol. & Exper. Therap. **80**:1, 1944.

high intakes of *l*-ascorbic acid did not affect the prothrombin time, Sullivan, Gangstad and Link [465] studied the effect of vitamin C on the fibrinogen content of plasma of normal and scorbutic guinea pigs and observed that with the onset of scurvy the fibrinogen increased noticeably. Restoration of normal fibrinogen levels occurred within two weeks after the addition of vitamin C to the basal diet.

Hemorrhagic Disease of the Newborn.—Further investigations dealing with the prothrombin status of the newborn continue to be reported. Both Pray [466] and Litchfield [467] confirm the observations of others that the administration of menadione to expectant mothers, either during the latter part of pregnancy or during labor, results in approximately normal prothrombin values in the infants and virtually eliminates the prolongation of the prothrombin times which usually occurs in the babies of untreated mothers between the second and fourth days of life. On funduscopic examination, Pray found notably fewer retinal hemorrhages among infants born of mothers treated before the onset of labor than among infants born of mothers treated only after labor had begun.

Hauser [468] is in accord with the opinion that treatment of the expectant mother is a better type of prophylaxis than is neonatal treatment of the child. He observed many hemorrhagic deaths despite neonatal therapy with vitamin K preparations. No authors report toxic deaths from large doses of vitamin K preparations.

Still an unexplained phenomenon is the fact that formula feedings during the first few weeks of life tend to counteract the usual neonatal hypoprothrombinemia. Pray [466] rejects as an explanation the hypothesis that by artificial feedings optimal conditions for the bacterial synthesis of vitamin K in the intestines are afforded. He was unable to demonstrate that administration of sulfaguanidine in full doses, beginning twelve hours after birth, had any inhibitory effect on the correction of the prothrombin time.

Mills, Cottingham and Mills [469] report that severe and fatal vitamin K deficiency can be produced in rats adapted to tropical heat by using vitamin K–free synthetic diets containing 0.5 per cent sulfaguanidine. At temperate coolness the manifestations are mild. The clinical

465 Sullivan, W. R.; Gangstad, E. O., and Link, K. P.: Note on Plasma Fibrinogen in Guinea Pig Scurvy, J. Biol. Chem. **152**:367, 1944.

466. Pray, L. G.: Hemorrhagic Disease of the Newborn: Prevention and Treatment with Vitamin K, Journal-Lancet **64**:1, 1944.

467. Litchfield, H. R., and others: Treatment of Prothrombinopenia with Water-Soluble Menadione, Am. J. Obst. & Gynec. **47**:642, 1944.

468. Hauser, F.: Vitamin K Prophylaxe bei 2520 Neugeborenen, Schweiz. med. Wchnschr. **73**:518, 1943.

469. Mills, C. A.; Cottingham, E., and Mills, M.: Environmental Temperature and Vitamin K Deficiency, Am. J. Physiol. **141**:359, 1944.

corollary of this is the finding that vitamin K deficiency is four times more prevalent among babies born in the Gulf States than among those born in the northern states.

Observations at some variance with these are reported by Lehmann,[470] who studied physiologic hypoprothrombinemia in 90 newborn infants through the first week of life. He found that babies born in the spring more commonly showed low values than those born in the summer. Admitting the difficulty of determining the level at which bleeding will occur, he nevertheless calculated that one third of the infants born in the summer and two thirds of those born in the spring would tend to bleed excessively if their vessels were damaged. He found that a 0.5 mg. dose of vitamin K analogue (sodium-2-methyl-1, 4-naphthohydroquinone disulfate) was as effective as a 5 mg. dose, whether given by mouth or intramuscularly. He points out that the factor determining the speed of increase in prothrombin is the reactive power of the liver, not the time taken for the vitamin to be absorbed.

Hardwicke[471] found the minimal effective daily dose of Synkavite (tetra sodium-2-methyl-1, 4-naphthohydroquinone) in the prevention of neonatal hypoprothrombinemia to lie somewhere between 0.005 and 0.0005 mg. Approximately 0.5 mg. of the test substance will apparently lower the excessively high prothrombin time and maintain it within normal range without further medication. No alteration in prothrombin time could be attributed to the administration to the mothers of several of the more common barbiturates.

Anticoagulant Therapy; Dicoumarin and Heparin. Vitamin K Preparations.—The successful use of heparin or dicoumarin in the prevention and treatment of thrombotic accidents is largely responsible for the current clinical interest in the anticoagulants. Beyond stating that the chemists are in agreement as to the synthesis and structural requirements for dicoumarin activity and that 3, 3′-methylene-bis (4-hydroxydicoumarin) is considered the most potent anticoagulant of the 4 hydroxycoumarin class,[472] no attempt will be made to review the extensive biochemical literature dealing with the anticoagulants.

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470. Lehmann, J.: Vitamin K as Prophylactic in 13,000 Infants, Lancet **1**:493, 1944.

471. Hardwicke, S. H.: Studies on the Minimal Effective Dose of a Water-Soluble Vitamin K Substitute in the Prevention of Hypoprothrombinemia in the Newborn Infant, J. Pediat. **24**:259, 1944.

472. Overman, R. S., and others: Studies on Hemorrhagic Sweet Clover Disease: Anticoagulant Activity and Structure in 4-Hydroxy-Coumarin Group, J. Biol. Chem. **153**:5, 1944. Rocha e Silva, M.: Estudos sobre a dicoumarina-3,3′-metilenobis-(4-hidroxicoumarina); historico e experiencias preliminares, Arq. Inst. biol., São Paulo **14**:293, 1943.

The modes of action of these agents are considered by Dyckerhoff [473] and by Douthwaite.[474] Dyckerhoff believes that dicoumarin exerts its anticoagulant effect in the first phase of clotting through incapacitating thrombokinase and that it does not enter into the second phase of clotting. Douthwaite holds to the more commonly accepted theory that dicoumarin exerts a specific action in the reduction of the prothrombin content of the blood while heparin acts by retarding conversion of prothrombin to thrombin.

Dicoumarin therapy in thrombotic emergencies is discussed in two papers by Evans.[475] The more detailed report is based on the observation of 46 patients treated over an eighteen month period. All received dicoumarin; 36 received supplementary heparin for the first two to five days (the latent period before which dicoumarin had not effectively lowered the prothrombin time), and 6 had paravertebral sympathetic block as well as dicoumarin. Hemorrhagic phenomena were evident eight times, but of 2 deaths, only 1 could unequivocally be attributed to dicoumarin. The contraindications to dicoumarin therapy are listed as hepatic damage, an already lowered prothrombin time or hemorrhagic diathesis. The necessity of a daily estimation of prothrombin time is emphasized. In this series pulmonary embolism occurred only once and was not fatal. The second paper is concerned with 55 patients considered as having potential pulmonary embolism, who were successfully treated with dicoumarin and heparin.

Barker [476] reports on the use of dicoumarin postoperatively for 624 patients at Mayo Clinic. One hundred and eleven patients had had pulmonary embolism or infarction and survived. In only 2 patients in this group did subsequent thrombosis occur, and in both of these the author feels the prothrombin time was not adequately elevated. Dicoumarin was given to 83 patients with postoperative thrombophlebitis. Further thrombophlebitis developed in 2 patients, but in none did embolism occur. Thrombosis or embolism did not occur in a group of 259 patients who had had abdominal hysterectomies and received, postoperatively, dicoumarin prophylactically. Dicoumarin was given prophylactically to 141 patients with such disorders as anemia, varicose

473. Dyckerhoff, H.: Ueber den Reaktionsmechanismus der Hemming der Blutgerinnung durch 33'-Methylen-di-(4-hydroxy-cumarin) genannt AP, Biochem. Ztschr. **316**:397, 1944.

474. Douthwaite, A. H.: Spoiled Sweet Clover and Other Anticoagulants, Guy's Hosp. Gaz. **58**:91, 1944.

475. Evans, J. A.: (*a*) Dicumarol Therapy in Thrombotic Emergencies, New England J. Med. **230**:131, 1944; (*b*) Anticoagulation Therapy of Postoperative Venous Thrombosis and Pulmonary Embolism, S. Clin. North America **24**:534, 1944.

476. Barker, N. W.: The Use of Dicumarol in Surgery, Collect. Papers Mayo Clin. **35**:414, 1944.

veins and obesity, because it was felt there was increased risk of postoperative thrombosis and embolism, and to 30 patients who with previous operations had had thrombophlebitis or pulmonary embolism. In no instance in these two groups did thrombosis or embolism occur. On the basis of this experience, Barker feels that adequate elevation of prothrombin time by the administration of dicoumarin is almost completely effective in the prevention of postoperative thrombosis and pulmonary embolism.

Gefter, Kramer and Reinhold [477] reported on a series of 34 patients with thromboembolic disease at the Philadelphia General Hospital who were treated with dicoumarin. Twenty-seven recovered, and 7 died. No changes attributable to dicoumarin were noted in the leukocyte count, hemoglobin content, blood sugar and urea nitrogen values, van den Bergh icterus index, retention of sulfobromophthalein or specific gravity, sugar or formed elements in the urine. No increase in antithrombin or decrease in platelets was observed. The only observed alteration was a decrease in prothrombin which, after a latent period, was reduced to levels of 25 to 30 per cent of normal in two days, with gradual rise to ± 50 per cent of normal in four weeks, despite continued therapy. The clotting time was uniformly increased. Bleeding times were variable and, except in 1 instance, within normal limits.

The only toxic manifestation observed by Gefter, Kramer and Reinhold was a hemorrhagic tendency. Withdrawal of the drug resulted in prompt recovery in 4 of the 5 patients with bleeding. The fifth required a transfusion of whole blood.

Thill and his associates [478] report a definite reduction in the incidence of formation of thrombi after the injection of a sclerosing agent, monoethanolamine oleate, in dogs prepared with dicoumarin in doses equivalent to therapeutic doses administered to human beings.

Davis and Porter [479] treated 43 patients with postpartum thrombosis with dicoumarin. Although the conditions varied so widely in severity that to find an exact parallel series for comparison was impossible, dicoumarin was believed to effect a slight but definite amelioration of pain and to be followed by a fairly rapid diminution in edema, with shortening of the average stay in the hospital. In all instances the drug was well tolerated. Of special interest was the lowering of the incidence of pulmonary embolism from 9 per cent to 4 per cent. These authors

477. Gefter, W. I.; Kramer, D. W., and Reinhold, J. G.: Clinical Experience with Dicumarol, Am. Heart J. **28**:321, 1944.

478. Thill, C. J., and others: Hemorrhagic Agent 3,3′-Methylenebis (4-Hydroxycoumarin): Its Effect in Prevention of Experimental Thrombosis, Proc. Soc. Exper. Biol. & Med. **54**:333, 1943.

479. Davis, A., and Porter, M.: Dicoumarin in the Treatment of Puerperal Thrombosis, Brit. M. J. **1**:718, 1944.

feel that dicoumarin therapy is of unequivocal value, at least in treatment of the type of patient on which they made their investigations. Eckstrom [480] believes that dicoumarin is generally of real value in preventing the extension of intravascular thrombosis.

Bollman [481] is in accord with this clinical observation despite the fact that experimentally he could find no evidence that dicoumarin or heparin modifies infarction or enhances the blood supply of the tissue after the blood vessels supplying the part have been occluded.

Essentially similar programs for dicoumarin dosage are outlined by Evans,[475a] Gefter, Kramer and Reinhold,[477] Eckstrom [480] and Bingham, Meyer and Howard.[482] An initial dose of 300 mg. is given, followed on the next day by 200 mg. with a subsequent daily dose of 0 to 200 mg., depending on the prothrombin time, which all authors agree must be determined daily. Allowance must be made for a latent period of twenty-four to seventy-two hours. The therapeutic level is reached when the prothrombin content of the blood is 25 to 50 per cent of normal.

Bingham, Meyer and Howard observed that the administration of dicoumarin may be safely combined with administration of heparin when prompt prolongation in the coagulation time is desired. With lengthening of the prothrombin time, evidence of the effectiveness of dicoumarin, the heparin may be discontinued.

Walker and Rhoads [483] found that only one half to one third the amount of heparin required to produce a given effect in the non-coumarinized person is needed to produce the same effect in the coumarized person, thus allowing, by means of intramuscular injection of heparin, a prolonged evenly maintained increase in blood coagulation time with avoidance of the inconvenience of continuous intravenous medication.

Bryson and Code [484] observed prolongation of the anticoagulant action of heparin given intramuscularly by suspension in beeswax-oil mixture, both in animals and in human beings. A distinct elevation in clotting time was consistently produced, which was demonstrable

480. Eckstrom, E. E.: The Clinical Use of Dicumarol: Report of Cases, Minnesota Med. **27**:455, 1944.

481. Bollman, J. L.: Failure of Dicumarol and Heparin to Modify Experimental Renal Infarction, Proc. Staff Meet., Mayo Clin. **19**:248, 1944.

482. Bingham, J. B.; Meyer, O. O., and Howard, B.: Studies on the Hemorrhagic Agent 3,3' Methylenebis (4-Hydroxycoumarin): A Report on Further Clinical Observations, Am. J. M. Sc. **205**:587, 1943.

483. Walker, J., and Rhoads, J. E.: Effect of Dicumarol on Susceptibility to Action of Heparin, Surgery **15**:859, 1944.

484. Bryson, J. C., and Code, C. F.: Prolonged Anticoagulant Action of Heparin in Beeswax Mixture, Proc. Staff Meet., Mayo Clin. **19**:100, 1944.

at four hours, reached its peak at twenty-four hours and persisted for three to five days.

Opinion is at variance as to the proper management of bleeding as a complication of overdosage with dicoumarin. Transfusion is favored by Jeanneret [485] as the only effective method of controlling the hemorrhage of overdosage with dicoumarin. In his experience therapy with a vitamin K preparation was equivocal, but 30 mg. was the largest dose of the vitamin K preparation he employed. With single 64 mg. doses (menadione bisulfite) Cromer and Barker [486] obtained satisfactory reduction in the prothrombin time of such patients, and transfusion was not necessary.

From another approach, Shapiro [487] has indicated the efficacy of vitamin K in controlling this type of bleeding. He was interested in the observation of Link and his associates that the quantitative degradation products of dicoumarin yielded 2 mols of salicylic acid and that in rats hypoprothrombinemia could be produced by salicylates and prevented by vitamin K. Shapiro therefore studied the course of 17 adult patients who were receiving salicylic acid in doses of 5 to 6 Gm. daily for the effect of the salicylate on the prothrombin time. Determinations of prothrombin time were done before and after supplementary doses of menadione in doses of 2 to 9 mg. daily. Before menadione was given, 13 patients displayed prolonged prothrombin times after three to five days of salicylate therapy. Menadione was protective. Since there are no fixed levels at which hypoprothrombinemia causes bleeding, Shapiro advises serial determinations of prothrombin time for patients receiving salicylate therapy. He feels that 1 mg. of menadione should be given prophylactically for each gram of acetylsalicylic acid. Complicating factors, such as fever, toxemia and limited nutrition, may make such adjuvants as ascorbic acid necessary.

A more potent vitamin K preparation for such therapeusis may be available soon. Mikhlin [488] reports the isolation from maize stigmas of an antihemorrhagic factor, for which he suggests the designation "vitamin K_3." This substance is effective in decreasing the prothrombin time not only in vitamin K–deficient subjects but in normal persons

485. Jeanneret, H.: Contribution à l'étude de l'action anticoagulante de la dicoumarine synthetique sur l'organisme humain, Schweiz. med. Wchnschr. **74**: 696, 1944.

486. Cromer, H. E., Jr., and Barker, N. W.: The Effect of Large Doses of Menadione Bisulfite (Synthetic Vitamin K) on Excessive Hypoprothrombinemia Induced by Dicumarol, Proc. Staff Meet., Mayo Clin. **19**:217, 1944.

487. Shapiro, S.: Studies on Prothrombin: The Effect of Synthetic Vitamin K on the Prothrombinopenia Induced by Salicylate in Man, J. A. M. A. **125**:545 (June 24) 1944; correction, ibid. **125**:923 (July 29) 1944.

488. Mikhlin, D. M.: Characteristics of Antihemorrhagic Factor from Maize Stigmata (Vitamin K_3), Biokhimiya **8**:158, 1943.

as well. It effects an acceleration of coagulation time to two to three times as fast as normal, coincident with a rise in prothrombin level by as much as 75 per cent.

Shlevin and Lederer [489] had an opportunity to study the histopathologic features in an instance of uncontrollable bleeding due to dicoumarin in which transfusion was of only temporary value. The features observed at necropsy were extreme engorgement of all the blood vessels, particularly the capillaries, arterioles and venules and a mild degree of cirrhosis of the liver. Whether the latter contributed to the toxicity of the dicoumarin is not known. McCarter, Bingham and Meyer [490] undertook to determine whether or not the liver was damaged by the use of dicoumarin. Large doses of dicoumarin were given to dogs, which were then killed. On histopathologic study there was found definite evidence of serious damage to small blood vessels, with disseminated gross and microscopic hemorrhages, and prominent swelling of the renal glomeruli, but no consistent lesions of the liver attributable to dicoumarin and no necrosis of the liver were found in any of the 29 dogs studied.

Quick [407] states that aside from depressing prothrombin, which is synthesized in the liver, dicoumarin appears to exert no deleterious effect on the liver.

The existence of a relation between hypoprothrombinemia and clinical hepatic disease is well recognized. Esculies [491] reviews the current knowledge concerning coagulation of blood with special emphasis on the role of vitamin K and the common sources of vitamin K deficiency. Although insufficient intake of vitamin K is rare because of the synthesis carried on by the intestinal flora, it may occur and is easily corrected by administration of vitamin K preparations. Deficient absorption of vitamin K and hepatic insufficiency are cited by Esculies as the two common sources of vitamin K deficiency. Kaufman [492] emphasizes the necessity of a healthy liver in the utilization of vitamin K.

No definite relation between the degree or duration of jaundice and the prothrombin level of the blood or the percentage of excretion of hippuric acid in patients with disease of the biliary tract could be demonstrated by Sinha.[493] He points out that in disease of the biliary

489. Shlevin, E. L., and Lederer, M.: Uncontrollable Hemorrhage After Dicoumarol Therapy with Autopsy Findings, Ann. Int. Med. **21**:332, 1944.

490. McCarter, J. C.; Bingham, J. B., and Meyer, O. O.: Studies on the Hemorrhagic Agent 3,3′ Methylenebis (4-Hydroxycoumarin): IV. The Pathologic Findings After the Administration of Dicumarol, Am. J. Path. **20**:651, 1944.

491. Esculies, J.: Coagulation sanguinea, Rev. san. mil., Asunción **139**:221, 1943.

492. Kaufman, J.: Prothrombin Studies, McGill M. J. **11**:74, 1941.

493. Sinha, S. K.: Significance of Blood Prothrombin Value in Diseases of Biliary Tract. J. Indiana M. A. **13**:67, 1943.

tract hypoprothrombinemia may be due to either of two factors: (1) a deficiency in the absorption of vitamin K, which can be corrected by either bile salts or a synthetic preparation of vitamin K (Kapilin), and/or (2) damage to the hepatic cells caused by pressure from the dilated intrahepatic biliary channels, the hypoprothrombinemia due to which is not correctable either with bile salts or with a vitamin K preparation.

Because of the apparent failure of severely damaged livers to respond to treatment with vitamin K preparations, Kinsey [494] attempted to prepare blood donors for such patients with large doses of menadione. The prothrombin content of the blood of such donors did not change with the administration of menadione. The benefit derived by the patient from such specially prepared donors was no different from that derived from unprepared donors.

The use of vitamin K preparations in other hemorrhagic situations has been investigated. Gubner and Ungerleider [495] report gratifying results in the control of menorrhagia not due to local pelvic abnormalities by administration of a synthetic naphthoquinone with pronounced vitamin K-like activity (Synkvite). Its beneficial effect is thought to be due to its action on prothrombin formation, since the latter is a sensitive index of hepatic integrity and since there is evidence that hepatic function is impaired at the onset of menstruation.

Farber and Miller [496] confirm previous reports of prothrombin deficiencies in tuberculous patients. Such deficiencies are most pronounced in bleeding patients but do not parallel the amount of blood loss and are definitely present in patients with constitutional symptoms. Thirty-three per cent of nonbleeding tuberculous patients and 58 per cent of the bleeding tuberculous patients studied had prothrombin deficiencies. Synthetic vitamin K restored the plasma prothrombin concentration of these patients but had no effect on their hemorrhages. Such instances of prothrombin deficiency are regarded simply as manifestations of a general nutritional deficiency.

Sharp, Wolter and Vonder Heide [497] present data based on the study of the prothrombin concentration and bleeding and clotting times for cutaneous blood of 221 patients with common blood dyscrasias.

494. Kinsey, R. E.: A New Aid in Control of Hemorrhage in Severe Damage to the Liver: Transfusions of Blood Fortified by Administration of Vitamin K to Donors, Arch. Int. Med. **73**:131 (Feb.) 1944.

495. Gubner, R., and Ungerleider, H. E.: Vitamin K Therapy in Menorrhagia, Indust. Med. **13**:301, 1944.

496. Farber, J. E., and Miller, D. K.: Nutritional Studies in Tuberculosis: Prothrombin Deficiency and Vitamin K, Am. Rev. Tuberc. **48**:406, 1943.

497. Sharp, E. A.; Wolter, J. G., and Vonder Heide, E. C.: Prothrombin in Disorders of the Blood, Am. J. Clin. Path. **14**:44, 1944.

Their data suggest that prothrombin deficiency of moderate severity may be present in the active phases of the common blood disorders, as may be abnormal bleeding from the cutaneous capillaries. No direct correlation could be established between the decreased prothrombin times and prolonged bleeding times, but the authors suggest that further study is indicated.

CHANGES IN THE BLOOD ASSOCIATED WITH INFECTION

The changes in the peripheral blood that accompany infection have long been recognized. It is emphasized, however, by many authors that serial determinations of the white cell count, particulary differential counts, are of infinitely more value in following the course of an illness than is any single set of determinations. The value of the hemogram in the interpretation of a variety of infections has been restated by several investigators.

In studying 62 cases of recurrent sore throat, Schilling and Jonssen [498] found repeated hemograms of value in differentiating allergic conditions from bacterial infections and so in choosing between medical and surgical management. Whereas those with bacterial infections showed the usual neutrophilic, monocytic and lymphocytic phases associated with infection, about half of the patients showed early lymphocytosis and high easinophilia, which were interpreted as indicating allergy. Relapses and complications tended to follow premonitory changes in the hemogram. Metke [499] considers that the hemogram is of value in determining the severity and development of complications in diphtheria. Serial white cell counts and differential counts for patients with pelvic inflammatory disease have been reappraised by Umbricht,[500] with the conclusion that, alone, such information is neither diagnostic nor prognostic but that, when correlated with clinical data, it may be a valuable aid in the proper management of the patient.

De Barros [501] accepts the concept of three stages portrayed by the hemogram during an infectious process: (1) a neutrophilic, or "fighting," phase, (2) a monocytic, or defensive, phase involving lymphocytoid, monocytoid or endotheloid cells of the reticuloendothelial system and (3) a lymphocytic, or recovering, phase. He notes that

498. Schilling, V., and Jonssen, K.: Angina als periodisch rezidvierende Infektion nach den Ergebnissen der biologischen Leukocyten-kurve, Folia haemat. **68**:4, 1944.

499. Metke, H.: Ueber die biologische Leukocyten-Kurve bei der Diphtherie, Folia haemat. **68**:72, 1944.

500. Umbricht, W.: Das weisse Blutbild bei entzündlichen gynäkologischen Erkrankungen, Schweiz. med. Wchnschr. **73**:719, 1943.

501. de Barros, N. V.: Estudo do hemograma emgeral; sua aplicação no puerpério normal e infectado, Folia clin. et biol. **13**:142, 1941.

in infections of the puerperium these changes are accompanied by a variable degree of anemia and a tendency toward an increase in platelets and suggests that the latter may account for the frequent association of thrombophlebitis. By means of the injection of blocking substances, he has been able to demonstrate hyperactivity of the reticuloendothelial system during pregnancy and postulates that this activity may explain the hyperbilirubinemia of pregnancy.

Luz and Siede [502] studied the blood picture in cases of epidemic hepatitis and found that at the onset there is a leukocytosis as in other infectious diseases. At first the entire leukocyte picture is affected, but with the onset of jaundice the count returns toward normal, later falling to subnormal values. These three phases are associated, respectively, with neutrophilic, lymphocytic and monocytic blood pictures. Highly characteristic of the disease is the appearance during the second phase of plasma cells of lymphoid origin. In the marrow an increase in myelopoiesis, such as is to be found in other infections, was observed.

Orens, Kelley and Agress [503] had the opportunity to study 43 patients with atypical pneumonia within a period of six weeks and were impressed not only by the constancy of the hematologic features but by the ways in which they differed from those in patients with bacterial pneumonias. During the first ten days the white blood cell count was normal or slightly below normal. Although the lymphocytes were unchanged or even slightly increased in number, the neutrophils showed some "shift to the left." Coincident with amelioration of the general symptoms and resolution of the pulmonic process, there occurred a variable leukocytosis associated with relative or absolute lymphocytosis. Frequently lymphocytes with morphologic changes similar to those seen in cases of infectious mononucleosis were observed. It is emphasized that the late development of leukocytosis is not an indication of relapse or complication and that for the patient with a history of recent infection of the respiratory tract showing an abnormal blood picture roentgenograms of the chest may be necessary to make the diagnosis of atypical pneumonia.

Further studies on the leukocytosis-promoting factor are reported by Menkin.[504] Whereas leukotoxine is said to be concerned only with local migration or diapedesis of polymorphonuclear leukocytes and so fails to alter the number of circulating leukocytes when introduced into the circulation, a leukocytosis-promoting factor can be

502. Luz, K., and Siede, W.: Das Blutbild der Hepatitis epidemica, Deutsche Ztschr. f. Verdauungskr. **7**:67, 1943.

503. Orens, M. H.; Kelley, R. W., and Agress, H.: Abnormal Blood Picture of Atypical Pneumonia, M. Bull. North African Theat. Op. **2**:56, 1944.

504. Menkin, V.: Further Studies on the Leukocytosis-Promoting Factor and on Necrosin in Inflammatory Exudates, Am. J. M. Sc. **208**:290, 1944.

obtained from inflammatory exudates. After injection of this substance, there appears in the marrow an increase in granulocytic forms and megakaryocytes and in the peripheral blood an increase in immature and nonfilamentous granulocytes as well as in the total leukocyte count. The author suggests the possibility of using this factor therapeutically in correction of various sluggish conditions of the bone marrow.

The association of eosinophilia with a variety of unrelated disorders is still not well understood. Its frequent occurrence in persons with schistosomiasis, ascariasis or hydatid infections is confirmed by Porrier,[505] who failed, however, to find any eosinophilia among 15 patients with amebic dysentery. Allen [506] has observed that in persons with hookworm infections eosinophilia may precede by two to six weeks the demonstration of ova in the stools. A case of chronic ulcerative colitis with eosinophilia of 51 per cent is reported by Stickney and Heck.[507] Burkhart and Montgomery [508] could find no correlation between eosinophilia of tissue and of blood in a variety of dermatoses. Schilling, Rothe and Zimmer [509] consider early eosinophilia important in the recognition of sporadic cases of scarlet fever. Stickney and Heck encountered the highest degree of eosinophilia in patients with allergic disorders, such as hay fever and asthma. However, among 418 patients with high grade eosinophilia no instances of pulmonary eosinophilic infiltration (Loeffler's syndrome) were observed. Pirkle and Davin [510] report eosinophilia of 33 per cent (total white blood cell count 8,800) in a 54 year old woman with migrating pneumonitis of eight months' duration. The patient had no signs of bronchial asthma. Schlecht [511] offers further evidence that Loeffler's syndrome is allergic in origin, comparing the histopathologic features with those observed in sensitized guinea pigs.

Of particular interest are the recent case reports following Weingarten's description in 1943 of an apparently new disease entity which

505. Porrier, M.: Considerations sur l'éosinophilie dans les maladies paracitaires, Bull. Soc. path. exot. **37**:59, 1944.

506. Allen, H. C.: Eosinophilia in the South Pacific, U. S. Nav. M. Bull. **42**:1241, 1944.

507. Stickney, J. M., and Heck, F. J.: The Clinical Occurrence of Eosinophilia, M. Clin. North America **28**:915, 1944.

508. Burkhart, R. J., and Montgomery, H.: Tissue Eosinophilia: Its Significance in Various Dermatoses, Proc. Staff Meet., Mayo Clin. **19**:38, 1944.

509. Schilling, V.; Rothe, I., and Zimmer, G.: Scharlach als in Schuken ablaufeude Infektion nach der biologischen Leukocytenkurve, Folia haemat. **68**:19, 1944.

510. Pirkle, H. B., and Davin, J. R.: Loeffler's Syndrome; Transient Pulmonary Infiltrations with Blood Eosinophilia, Am. Rev. Tuberc. **50**:48, 1944.

511. Schlecht, H.: Das allergische, eosinophile Lungeninfiltrat, Deutsche med. Wchnschr. **70**:189, 1944.

he thought to be peculiar to certain parts of India, characterized by severe spasmodic bronchitis, malaise, leukocytosis and high eosinophilia. The cause is unknown, but it is not believed to be an allergic state. The response to arsenic is phenomenal, with disappearance of the constitutional and pulmonary symptoms and subsidence of the eosinophilia. Increases in all manifestations following the initial injections of neoarsphenamine have been described, after which dramatic cures ensue. Parsons-Smith [512] reports from Egypt an instance of this so-called tropical eosinophilia in a 28 year old English airman. The maximum leukocyte value and eosinophil percentage were 20,000 per cubic millimeter and 34 per cent, respectively. The clinical course and response to neoarsphenamine were typical.

Shah [513] reported the case of a 22 year old Hindu man with fever, malaise and cough. Rales and rhonchi were present throughout the lungs, and there was roentgenographic evidence of peribronchial infiltration. The white blood cell count was 19,000 per cubic millimeter, and the eosinophils were 70 per cent. The symptoms promptly subsided after injections of diethylamine oxyacetylaminophenylarsonate (acetylarsen), although mild eosinophilia persisted.

Another instance of febrile pulmonary disease associated with leukocytosis and extreme eosinophilia which responded promptly to treatment with an organic arsenic compound is reported by Chakravarty and Roy.[514] Emerson [515] reports a case wherein all the signs and symptoms of the tropical eosinophilia coincident with severe intercurrent infection appeared eight months after the patient returned to the United States from India. Carbarsone therapy effected the complete disappearance of all evidence of eosinophilia.

RELATION OF THE THYROID GLAND TO HEMOPOIESIS

Because of conflicting reports regarding the changes in hemopoiesis in patients with thyroid dysfunction, Wilson [516] undertook a study of the blood and bone marrow of a series of 31 patients suffering from severe thyrotoxicosis and of 1 patient suffering from myxedema. The changes in the blood and bone marrow and other changes produced in rats by thyroidectomy and by the injection of thyroxin were also investigated. The 31 untreated thyrotoxic patients showed mild

512. Parsons-Smith, B. G.: Tropical Eosinophilia, Lancet **1**:433, 1944.

513. Shah, R. L.: A Case of Pseudo-Tuberculosis of the Lungs with Eosinophilia, Indian M. Gaz. **78**:597, 1943.

514. Chakravarty, U. N., and Roy, S. C.: A Case of Tropical Eosinophilia? Indian M. Gaz. **78**:596, 1943.

515. Emerson, K., Jr.: Tropical Eosinophilia, U. S. Nav. M. Bull. **42**:118, 1944.

516. Wilson, T. E.: The Thyroid Gland and Haemopoiesis, M. J. Australia **1**:261, 1944.

anemia and increased cellularity of the marrow affecting all the cells except the monocytes. The increased cellularity of the marrow was not reflected in the peripheral blood. Examinations of blood and bone marrow repeated two to three weeks after thyroidectomy on 10 patients showed no significant changes. The single patient with myxedema studied showed mild anemia and decreased cellularity of the marrow. In rats transformed into cretins by thyroidectomy mild anemia and hypocellularity of the marrow developed, whereas adult thyroidectomized rats had normal blood values and rats injected with thyroxin showed increased cellularity of the marrow. The author reviews the various explanations of the role of the thyroid in hemopoiesis and concludes that the thyroid gland exercises a nonspecific control over the metabolism of the elements of the marrow, resulting in their hyperplasia in thyrotoxicosis and in their hypoplasia in cretinism and myxedema.

You, Kwang and Chu [517] studied the effects of thyroidectomy and thyroid feeding in rabbits. Thyroidectomized animals showed, up to the fifth week, a progressive fall in the hemoglobin content and red blood cell count, associated with increased erythrocyte fragility and reticulocytosis. Subsequently their values were stabilized, with significantly lower red blood cell counts and hemoglobin values. There was, however, a slight decrease in the number of reticulocytes, and a slight decrease in fragility of the red cells. The finding of reticulocytosis associated with increased red cell fragility in thyroidectomized animals and of the reverse in thyroid-fed animals suggested to the authors that the thyroid hormone may exert a protective action on erythrocytes, which would otherwise be subject to more rapid destruction.

That endocrine glands other than the thyroid may exert some control over hemopoiesis is suggested by the report of Armstrong.[518] His patient, a middle-aged woman, had severe, long-standing myxedema associated with anemia. For five years large doses of thyroid had been given daily without correction of the anemia. The administration of testosterone propionate with desiccated thyroid was followed by subjective and hematologic improvement.

METHODS AND MISCELLANEOUS MATERIAL

Much attention has recently been directed toward standardization of various hematologic laboratory procedures. King, Gilchrist and Delory [519] are among those who have attempted to evaluate the accuracy

517. You, S. S.; Kwang, D. R., and Chu, J. P.: The Influence of the Thyroid Gland on the Blood Picture in the Rabbit, Proc. Chinese Physiol. Soc. **2**:50, 1944.

518. Armstrong, C. D.: Case of Myxedema with Ascites, Anemia, Myxedema Heart, Angina and Delayed Relaxation of Reflexes, with Note on Therapeutic Effects of Testosterone Propionate, Stanford M. Bull. **2**:25, 1944.

519. King, E. J.; Gilchrist, M., and Delory, G. E.: Accuracy of Haemoglobin Methods, Lancet **1**:239, 1944.

of the current methods of determination of hemoglobin content. They found that the least satisfactory methods were those which depend on matching a standard by dilution, such as the Haldane and Sahli procedures. The photoelectric and photometric methods possessed high degrees of accuracy. The cyanmethemoglobin procedure was the most accurate method tested and is recommended by these authors for research purposes. Although it is simple and easy, the hazard involved in the routine use of cyanide is recognized and must be considered before the method is accepted for general clinical use. The alkaline hematin and carboxyhemoglobin methods were slightly less accurate but are considered satisfactory for most purposes. King and his associates give the technics of these various procedures. Horecker and Brackett [520] report a spectrophotometric method for the simultaneous determination of methemoglobin, carbonylhemoglobin and total hemoglobin, said to be accurate to within about 1 per cent. The performance of the method with the Coleman Spectrophotometer is described. The details of the photoelectric method for routine estimates of hemoglobin content are outlined by Reeve,[521] together with an analysis of the common sources of error. The copper sulfate method of Phillips and van Slyke for determining the specific gravity of blood has been adapted to determinations of hemoglobin content, with an accuracy reputedly within 2 per cent of the value as determined by oxygen-carrying capacity.

Duffie [522] describes a plungerless, one cup colorimeter in which a green filter incorporated in the eyepiece absorbs red. The instrument is designed for reading hemoglobin values as well as for many chemical determinations on the blood; it is small, simply constructed and easily adjusted, as well as accurate.

Attempts in the past to determine red blood cell counts other than by direct enumeration have not met with much success. However, Parker, Spicer and Porter [523] present a method for computing the red cell count on the photoelectric colorimeter. Satisfactory correlation with hemocytometer values are offered for 25 patients. Caution is expressed in reference to accepting colorimeter readings if obvious microcytosis or macrocytosis is observed when examining the stained

520. Horecker, B. L., and Brackett, F. S.: A Rapid Spectrophotometric Method for the Determination of Methemoglobin and Carbonylhemoglobin in Blood, J. Biol. Chem. **152**:669, 1944.

521. Reeve, E. B.: Observations on Photo-Electric Estimation of Total Haemoglobin, J. Path. & Bact. **56**:95, 1944.

522. Duffie, D. H.: Hemoglobin Estimation by Revolutionary Colorimetric Method of Kennedy, with Further Report on Simple Instrument for Facilitating Utilization of Principle, J. A. M. A. **126**:95 (Sept. 9) 1944.

523. Parker, G. M.; Spicer, H. E., and Porter, H.: Method for Computing Red Cell Count on Photoelectric Colorimeter, Am. J. Clin. Path. **8**:37, 1944.

film. The authors, however, consider the method simple and rapid and suitable for routine counts.

Further observations are reported by Mallery and Randolph [524] on the use of a diluting fluid for white blood cells consisting of 0.1 per cent eosin and 0.1 per cent methylene blue (methylthionine chloride) dissolved in equal parts of propylene glycol and water for simultaneous white blood cell counts and counting chamber differential counts. For general purposes the results are said to compare favorably with those obtained with the use of standard acetic acid diluting fluid and Wright-stained cover slip films.

The usual multiple tube method of determining erythrocyte fragility with macroscopic reading is criticized by Fennel [525] for its well known inconvenience and obvious dependency on the personal equation in interpretation. A simple one tube method for "screening" of patients with abnormal fragility is outlined, together with the technic of a more elaborate serial dilution method, using pipetted amounts of blood instead of drops and the photocolorimeter for reading, thereby eliminating the personal equation. Fennel states that decreased erythrocyte fragility is more common than increased fragility.

Hegglin and Maier [526] outline a specific test for the recognition of Marchiafava's syndrome based on the concept that the "heat resistance" of the erythrocytes of patients with this disease is less than normal, so that in the presence of complement hemolysis takes place and the degree of hemolysis increases as the temperature rises.

Success in the staining of sections of bone marrow with Giemsa stain is reported by Lewis,[527] who suggests that the method should work equally well on marrow films. The technic is given. Arnold [528] describes a method of preparing and staining bone marrow films with equal parts of Wright's and Leishman's stains or with Jenner-Giemsa or May Grunwald-Giemsa stains. The need for meticulously clean glassware and great technical care is emphasized.

A simple method of venipuncture is outlined by Markuson [529] whereby the blood is drawn into a vial in which mild negative pressure

524. Mallery, O. T., Jr., and Randolph, T. G.: The Effect in Vitro of Propylene Glycol on Leucocytes, J. Lab. & Clin. Med. **29**:203, 1944.

525. Fennel, E. A.: Erythrocyte Fragility, Am. J. Clin. Path. **8**:21, 1944.

526. Hegglin, R., and Maier, C.: "Heat Resistance" of Erythrocytes: Specific Test for Recognition of Marchiafava's Anemia, Am. J. M. Sc. **207**:624, 1944.

527. Lewis, E. J.: Giemsa Stain for Bone and Bone Marrow Sections, Canad. J. Med. **6**:5, 1944.

528. Arnold, G. M.: A Method of Preparing and Staining Bone Marrow Smears, Canad. J. Med. **6**:47, 1944.

529. Markuson, K. E.: A New Technique in Drawing Blood for Serodiagnostic Tests: Use of the Hemospast, J. Indiana M. A. **37**:400, 1944

has been produced. The details for preparation of the necessary equipment are given. The method obviates the obvious handicaps in the common syringe-needle method of aspiration, requires no special skill and is advocated for mass testing. The name given to this device is the "hemospast."

The difficulty frequently encountered in giving fluids, electrolytes or blood intravenously to young or debilitated patients has led to a search for some other method of introducing these substances into the circulation. Turkel and Bethell [530] offer a solution to this problem in the description of a new and simple instrument for the administration of such fluids through the bone marrow. It may be used for sternal infusions in treatment of adults and older children and in the treatment of younger children for intratibial infusions. Arbeiter and Greengard [531] report on the successful use of infusions in tibial bone marrow in treatment of 34 young children, using primarily the needle described by Turkel. Meola [532] considers infusions in marrow of inestimable value because of the ease and expediency with which they are done. The indications, fluids used and ages and conditions of the patients for 326 such infusions are recorded. Parada [533] also reports favorably on the use of intramedullary transfusion in children, giving details of his technic.

Although the blood sedimentation test was not introduced to medical practice until 1921, it had been observed by physicians for many centuries that there was an increased plasma layer in blood "drawn" for many conditions having little in common save fever. Despite its lack of specificity, as an auxiliary method in diagnosis much importance is attached to this simple procedure. In a series of 270 patients, 146 of whom were tuberculous, Crowe [534] found the sedimentation rate in 69 per cent paralleled the presence or absence of pulmonary disease, as determined by other criteria. Cimmino [535] found increased sedi-

530. Turkel, H., and Bethell, F. H.: A New and Simple Instrument for Administration of Fluids Through Bone Marrow, War Med. **5**:222 (April) 1944.

531. Arbeiter, H. J., and Greengard, J.: Tibial Bone Marrow Infusions in Infancy, J. Pediat. **25**:1, 1944.

532. Meola, F.: Bone Marrow Infusions as a Routine Procedure in Children, J. Pediat. **25**:13, 1944.

533. Parada, L. S.: Transfusión de sangre en los niños por vía intramedular osea, Pediat. Américas **2**:249, 1944.

534. Crowe, M.: The Blood Sedimentation Test in a Tuberculosis Dispensary, Irish J. M. Sc., 1944, p. 531.

535. Cimmino, V.: Studio sulla velocita di sedimentazione in Eritrea; la V. di S. nella tuberculosi pulmonare e nella lues, Boll. Soc. ital. di med. e ig. trop. **2**:55, 1943; Studio sulla velocita di sedimentazione in Eritrea; la velocita di sedimentazione nella febbre ricorrento, ibid. **2**:76, 1943; Studio sulla velocita di sedimentazione in Eritrea; la V. di S. nel tifo esantematico, ibid. **2**:64, 1943.

mentation rates in patients with pulmonary tuberculosis and observed rapid rates not only in patients with untreated syphilis but also in those with syphilis resistant to treatment. He reports an increase in the sedimentation rate during the second week of illness with typhus, with a slow return to normal during convalescence. He observed no relation between the severity of the typhus, the intensity of the Weil-Felix reaction and the speed of sedimentation. In patients with relapsing fever an increase in the sedimentation rate occurred not only during episodes of fever but also during the apyrexic periods. Although specific therapy cures the relapsing fever, a long interval elapses before the sedimentation rate returns to normal. This the author attributes to the prolonged action of the arsenobenzene preparations used in the treatment of the disease. Mendel and Korenberg [536] report further observations in support of the maintenance of elevated sedimentation rates of blood removed from patients with cancer, Hodgkin's disease and leukemia in contrast to that observed in persons with nonmalignant pathologic conditions. He therefore advocates twenty-four hour observations of the sedimentation rates as a diagnostic adjunct. The sedimentation rates of 125 patients with poliomyelitis were studied by Dokow.[537] Sedimentation rates of 42 per cent of the patients were normal and of 58 per cent increased, and they never decreased. Great acceleration was rare. There was no correlation between the sedimentation rate and the extent of the clinical process.

Using both the Westergren macromethod and the Kato micromethod, McKinley and Jackson [538] found that the sedimentation test was of definite value in the evaluation of the clinical course of patients with rheumatic fever. The micromethod, avoiding venipuncture, was more convenient when the determinations were made by an experienced technician but was less reliable in examination of acutely ill patients. However, values obtained by either method paralleled satisfactorily the course of the disease process. A simple method of determining sedimentation rate involving the use of only 0.3 cc. of blood, which may be obtained from the finger tip, is outlined by Phillips.[539]

A new application of the sedimentation rate is offered from experience in the armed services. An epidemic of mumps among navy per-

536. Mendel, D. L., and Korenberg, M.: Maintenance of the Sedimentation Rate of Erythrocytes in Cases of Cancer, Hodgkin's Disease, and Leukemia, Canad. M. A. J. **51**:353, 1944.

537. Dokow, F.: Ueber Blutbild und Erythrocytensenkungsgeschwindigkeit bei Poliomyelitis acuta anterior, Inaug. Dissert., Med. Fak. **94**:1, 1937.

538. McKinley, J. B., and Jackson, R. L.: Comparison of Westergren and Kato Erythrocyte Sedimentation Rate Readings; Relation to the Clinical Status of Children with Rheumatic Fever, Am. J. Dis. Child. **67**:474 (June) 1944.

539. Phillips, E. C.: Sedimentation Rates, Pub. Health Nursing **36**:474, 1944.

sonnel enabled Candel and his associates[540] to study 37 cases, 13 uncomplicated, 10 complicated by meningitis and 14 complicated by orchitis. Study of the erythrocyte sedimentation rates showed no significant deviation from normal in cases of uncomplicated mumps or of mumps complicated by meningitis, but a decided increase in sedimentation rate occurred in patients with mumps complicated by orchitis. The rise in sedimentation rate may precede the appearance of orchitis and may persist for weeks after recovery, possibly denoting the persistence of an inflammatory or degenerative process in the testes.

It has been repeatedly observed, especially in treatment of infants with splenomegaly, that subcutaneous injections of epinephrine hydrochloride produce an outspoken increase in the number of circulating erythrocytes. These increases are usually associated with obvious shrinking of the spleen. Watson and Paine,[541] therefore, undertook to examine blood from both the splenic artery and the splenic vein, before and after injections of epinephrine, of 9 patients at the time of splenectomy for acquired and familial hemolytic icterus, chronic myeloid leukemia with associated mild hemolytic anemia and thrombocytopenic purpura. In general, splenic venous blood showed a great increase in erythrocyte concentration after injection of epinephrine into the artery. Associated with this was a decrease in mean corpuscular hemoglobin concentration and also an increase in fragility and spheroidicity. The exact cause of this decrease in hemoglobin concentration is unknown. It was thought that it might be due to an intracorpuscular degeneration of a fraction of the hemoglobin in the intact erythrocytes during the period of their sequestration in the spleen, analogous to that observed when significant increases of bilirubin and iron in the supernatant plasma occur after incubation of sterile blood for as little as six hours.

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540. Candel, S.; Wheelock, M. C.; Turk, M. P., Jr., and Smoot, J. L.: Erythrocyte Sedimentation Rate in Mumps and Its Complications, U. S. Nav. M. Bull. **42**: 571, 1944.

541. Watson, C. J., and Paine, J. R.: A Study of the Splenic Venous Blood, with Particular Reference to the Hematocrit Percentage and the Hemoglobin Concentration of the Erythrocytes, Before and After Splenic Arterial Injection of Adrenalin, Am. J. M. Sc. **205**:493, 1943.

Book Reviews

Health Instruction Yearbook, 1945. Edited by O. E. Byrd, Ed.D., Associate Professor of Hygiene, School of Health, Stanford University. Price, $3. Pp. ix + 344. Stanford University, Calif.: Stanford University Press, 1945.

While browsing in his local public library this reviewer first encountered this volume. He liked its looks, the systematic way in which the contents were arranged, the index and the short digests of a large amount of literature. For the book discusses, in the form of abstracts, almost every paper pertaining to public health which was of interest during the past year.

He discovered that *The Journal of the American Medical Association* knew the series and had reviewed the two first volumes.

Of the first, *The Journal* said (**124**:131 [Jan.] 1944) that it was an interesting beginning: To be sure, such books had been written before and had been unsuccessful. Now, a recent upsurge of interest in public health and in health education perhaps offered this particular yearbook a propitious start; in any event, it commenced in an interesting and useful fashion.

Toward the second volume *The Journal* (**126**:799 [Nov.] 1944) was more gracious. By now the potential usefulness of such a yearbook was better established, especially since it continued to be edited with particularly good judgment. On the whole, *The Journal* said that the two volumes together constituted a valuable source of reference.

The ARCHIVES is glad to have met the third volume. We believe that the series should find a place in every medical library to which medical students have access and that many practicing physicians can learn much from it. Medical libraries unacquainted with the undertaking will do well to obtain copies of all the volumes so far in print; for, so long as present editorial standards are maintained, each subsequent volume will be worth shelving.

What People Are; A Study of Normal Young Men. By Clark W. Heath, M.D., and others. Price, $2. Pp. xvi + 141, with illustrations. Cambridge, Mass.: Harvard University Press, 1945.

Seven years ago an institution known as the Grant Study was established at Harvard University "to achieve a more thorough understanding of human behavior characteristics and to interpret them more precisely and wisely." The work began with a study of a selected group of young men in which not only their physical characteristics were analyzed but also their psychologic makeup, in order that they might receive advice concerning how best to pursue successful careers. This book gives the results of what has been accomplished so far.

It is an interesting compilation, combining physical and clinical measurements in common clinical use with more imponderable mental reactions and leading to the general conclusion that within every person, whether he is classified by some scheme as "normal" or not, lie the potentialities of better integration and better conduct of life.

The variations encountered in measuring healthy young men in such ways are interesting: the differences in appearance, for example, that are so obvious between a man with strong masculine makeup and one who has weak masculine components. The methods that were employed in measuring mental attributes are ingenious and will serve as a guide to future studies. On the whole, many physicians, and certainly all directors of health departments in schools and colleges, will find this short volume worthy of careful study. It is a stimulating and interesting bit of medical literature.

The Care of the Neurosurgical Patient. By Ernest Sachs, M.D. Price, $6. Pp. 268, with 177 illustrations. St. Louis: C. V. Mosby Company, 1945.

The author of this book, as is well known, is a professor of neurologic surgery, an eminent writer and a skilled clinician. To read his book is a joyful experience because it contains so much good teaching and valuable clinical observations, and at the same time is so readable.

The preface states that it was prepared especially for house officers and for the young surgeons who are hoping to enter the specialty of neurosurgery. In reality, it is a text that will be appreciated fully as much by internists or radiologists, or even by pathologists. The care of the patient is discussed; diagnostic methods and preoperative and postoperative care are thoroughly described, and the problems which the expert neurosurgeon encounters most frequently are well analyzed.

The print is excellent; the illustrations—of which there are many—are apt and tend to clarify the text, and the bibliography is carefully selected for the reader who wishes more detailed knowledge. On the whole, here is a volume which, deservedly, is bound to achieve wide popularity.

Prescribing Occupational Therapy. Second Edition. By William Rush Dunton Jr., M.D. Price, $2.50. Pp. 151. Springfield, Ill.: Charles C Thomas, Publisher.

This well arranged little book could be read with advantage by every medical student and physician. After discussing the general philosophy of occupational therapy the author gives details of application for various categories of patients, such as medical, surgical, mental, orthopedic and cardiac. There is a bibliography after each chapter which brings the subject fully up to date. There is an index.

News and Comment

AMERICAN SOCIETY FOR RESEARCH IN PSYCHOSOMATIC PROBLEMS

The annual meeting of the American Society for Research in Psychosomatic Problems will be held at the Hotel Pennsylvania, New York, May 11 and 12, 1946. "Contributions of Military Medicine to Psychosomatic Medicine" will be discussed in the morning and "Psychosomatic Aspects of Orthopedic Practice" in the afternoon. After the annual dinner an illustrated parody on "New Advances in Psychosomatic Investigative Technic," by Dr. Bertram D. Lewin, will be presented. On May 12 there will be volunteered contributions.

Because of space limitation, reservations should be made at least two weeks prior to the meeting. Further information may be procured from Dr. Roy G. Hoskins, chairman, program committee, 714 Madison Avenue, New York 21.

CORRECTION

Attention has just been called to the fact that the name of one of the authors—Dr. Morgan Swirsky—was omitted from the article entitled "Extragenital Chorionepithelioma in the Male," which was published in the November-December issue of the ARCHIVES OF INTERNAL MEDICINE (**76**:347, 1945). The names of the authors there given were Hyman M. Chernoff, M.D.; Theodore S. Evans, M.D., and Charles J. Bartlett, M.D. Dr. Morgan Swirsky's name should be added to the names listed.

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